METALLATION, CONFORMATIONAL ANALYSIS, HYDROGEN EXCHANGE AND REARRANGEMENT IN AMIDES

BY

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To my wife

Sutharchana Devi

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Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

METALLATION, CONFORMATIONAL ANALYSIS, REARRANGEMENT AND HYDROGEN EXCHANGE IN AMIDES

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Major Department: Chemistry

Amides are known to stabilize a carbanion α to the nitrogen. The synergistic effect of amide groups on carbanion stability was previously unknown. Thus, metallation of 1,3-diacylimidazolidines, 1,3-diacylhexahydropyrimidines and 1,3,5-triacylhexahydro-sym-triazines has been investigated. The results show no substantial additional stabilization by the second amide function. This might be due to steric crowding caused by the alkyl or aryl group of the acyl units.

Little was known about restricted rotation around C-N bonds of bis- and trisamides. A ^{1}H and ^{13}C variable temperature NMR study of acyl derivatives of cyclic secondary amines, imidazolidines, hexahydropyrimidines and hexahydro-sym-triazines, has been performed. Conformer populations were determined at different temperatures and their barriers to rotation around the amide C-N bond

calculated from their coalescence temperatures. A possible mechanism of conformational interconversion was predicted from the observed spectral change with temperature.

Base catalyzed hydrogen exchange on various N- and O-substituted 4-pyridones, including vinylogous amides, was investigated. Exchange of the 2,6-protons of N-aryloxy- and N-arylthiomethyl-4-pyridones was five times faster than that of N-methyl-4-pyridone, indicating the participation of the heteroatom in the exchange reaction. This participation is very clear in N-(4-pyridinoxymethyl)-4-pyridone which exchanges the pyridone 2,6-protons in addition to the pyridine 3,5-protons at temperatures between 40-50°C. Studies of model compounds such as 2-(4-pyridinoxymethyl)ethanol, confirm this explanation.

The mechanism for the thermal rearrangement of alkyl groups from oxygen to nitrogen in 4-pyridones had been proposed but not proved. A mechanistic study of the thermal rearrangement using the labelled compound N-(3,5-dideutero-4-pyridinoxymethyl)-2,6-dideutero-4-pyridone and its unlabelled analogue was investigated. Based on the product ratios obtained by mass spectrometry the rearrangement was found to be intermolecular.

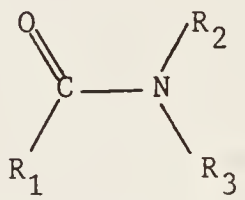
CHAPTER 1

GENERAL INTRODUCTION

For nearly two centuries the study of amides has proved to be a rapidly expanding and intriguing area for investigation. Not only is the amide moiety an important constituent of many biologically significant compounds but an understanding of its formation, properties and reactions is essential for the dynamic growth of peptide chemistry. This holds great promise for major discoveries essential to human well being. Besides their biological importance, amides are of fundamental chemical interest because of their distinct physical and chemical properties related to the conjugation between the nitrogen lone pair electrons and the carbonyl π bond. It is appropriate to survey briefly the chemistry of amides prior to the discussion of this work. The following discussion on amides can not hope to be comprehensive but is intended to give some idea of the trends observed in this work.

1.1. Structure of the Amide Group

The physical structure of the amide group has been the subject of much recent work. Reviews on the molecular and electronic structure [70MI1] and nuclear magnetic resonance (NMR) properties [70CR517] summarize much of the new developments including the shape and stereochemistry of the amide group and spectroscopic properties.



(1.1)

1.1.1. Geometry

The molecular structure of the amide group in both the condensed and gaseous phases is fairly well established. However, several complicating features need to be taken into consideration when interpreting physical measurements on these compounds. One of these features is the partial double bond character of the C(O)-N bond resulting from delocalization of the nitrogen lone pair electrons into the π-system of the carbonyl bond. There are two extreme valence bond forms, zero conjugation (1.2a) and complete conjugation (1.2b) as shown in Figure 1.1.

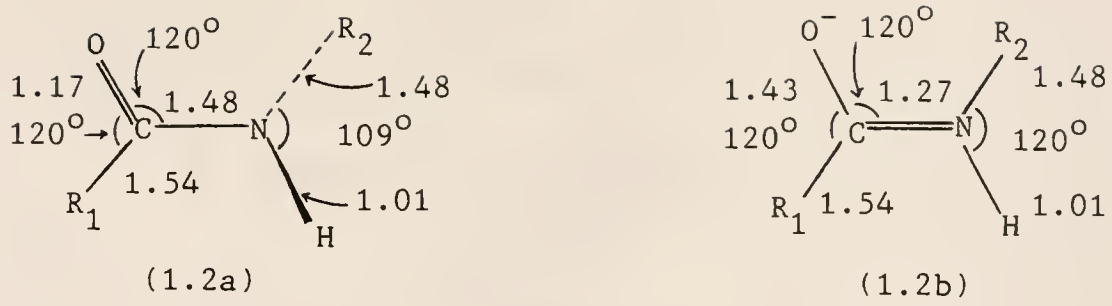


Fig. 1.1 Major Resonance Forms for Amides Showing Predicted Bond Lengths (Å) and Bond Angles [79MI1].

X-ray diffraction studies of crystalline amides [70MI1] show a fairly constant geometry for the amide group. All the heavy atoms of the amide functionality are essentially in a plane. The mean values of the bond lengths and the bond angles are given in (1.3) (Figure 1.2).

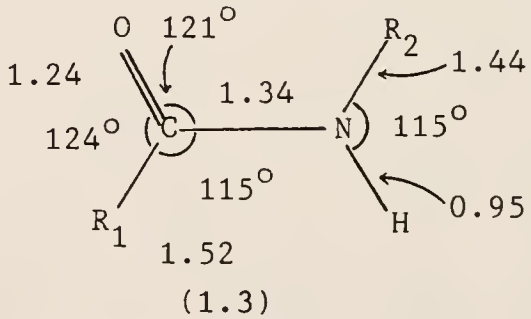


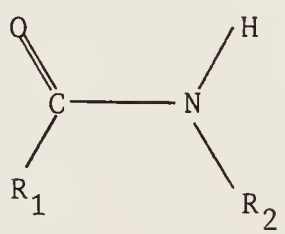
Fig. 1.2 Mean Values of Bond Lengths (Å) and Angles in Crystalline Amides [79MI1].

The gas phase microwave and electron diffraction studies [70MI1], [74BCSJ631] compared to X-ray diffraction

studies of crystalline amides show that the bond angles remain essentiallty the same but the C-O bond length is reduced to 1.19-1.20 Å with concomitant lengthening of the C-N bond to 1.36-1.37 Å. This implies that there is a greater contribution from structure (1.2a) in the gas phase than in the solid phase.

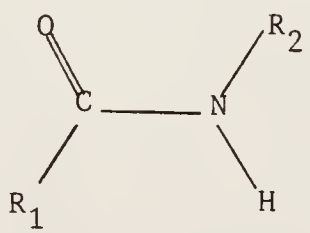
1.1.2. Rotational Barrier

One of the most fundamental concepts in all investigations of structure is conformational analysis. In amides the consequence of partial double-bond character is the existence of conformational isomers (1.4) and (1.5), arising from the lack of free rotation about the C(O)-N bond. The existence of these isomers has been established by dipole moment measurement [64JAM337], infrared and Raman spectroscopic studies [70MI1] and by nuclear magnetic resonance (NMR).



cis (E)

(1.4)



trans (Z)

(1.5)

Amides have been intensively studied by NMR [70CR517]. Though most of these studies have dealt with rotational isomerization about the C(O)-N bond, considerable attention has also been given to chemical shifts, J couplings, proton exchange and association of the amides.

The effect of solvent and concentration on the free energy of activation (barrier) has been studied [65JCP3320, 70MI1]. The barrier increased with increase in solvent polarity. Similarly, the barrier is also increased with concentration. In both cases the ground state was expected to be stabilized by polar solvents and by dipole-dipole association at higher concentrations.

The effect on the barrier of substituents on both the nitrogen and the carbonyl group has been investigated and a number of references are available [70CR517, 74JAM2260, 67JAM4300].

1.2. Preparation of Amides

The amide linkage can be assembled in several ways, and this is reflected in the variety of methods available for the synthesis of amides [70MI1], their cyclic analogues the lactams [70MI1], and the vinylogous amides the 4-pyridones [74MI1].

1.2.1. Acyclic and Cyclic Amides

The most common synthetic pathway for amides themselves is that of bond formation between a carbonyl-carbon atom and an amino-nitrogen atom, and this is achieved by treatment of either ammonia or a primary or a secondary amine with an acylating agent. This yields a primary, secondary, or tertiary amide, respectively. The other common pathway for amide formation is the introduction of a carbonyl group into an unsaturated amino compound, for example, partial hydration of either a nitrile or an imidoyl derivative, producing the primary or secondary amide, respectively. The imidoyl derivative itself can in principle be obtained by alkylation of the nitrile. Methods of N-alkyl or N-aryl bond formation (other than direct replacement of the amido-H) principally require rearrangements such as in the Schmidt or Beckmann reactions. Synthesis of amides by formation of the bond between an alkyl or aryl group and the carbonyl carbon atom is the most difficult method to achieve and requires more specific reagents such as ketenes, isocyanates, and isocyanides. Neither direct oxidation nor reduction of suitable precursors has wide applicability in amide synthesis.

The synthesis of lactams (cyclic amides) generally follows the same procedures as for acyclic amides except

where special factors such as ring size and ease of reaction are concerned. Further modification of the parent lactam can be achieved by alkylation of the nitrogen atom, and sometimes of the carbon α to the carbonyl group using conditions similar to those for acyclic amide alkylation. The new method available for α-metallation of amides (α to nitrogen) followed by electrophilic addition giving α-electrophile substituted amides [84CR471]. This was one of the methods used for preparing α-metalloamine synthetic equivalents (for further details see Chapter 2).

1.2.2. Vinylogous Amides

4-Pyridones can be prepared in two basic ways, by ring closure reactions and by the transformation of other ring compounds. For example, in the latter case 4-pyrones can be transformed into 4-pyridones just by treating the corresponding 4-pyrones with the required amines. However, the ring closure reactions yielding 4-pyridones have many more possiblities, using (i) a triketone or a ketoaldehyde and ammonia [65JAM3186], (ii) β-diketones and aromatic Schiff bases [69BCSJ1357], (iii) β-diketones and benzonitrile [69BCSJ2389], (iv) di-1-propynyl ketone and primary amines [60A1409], and (v) primary and secondary enamines, prepared from ethyl acetoacetate or β-diketones, with diketene [69M132].

1.3. Reactivity of Amides

Since all three atoms in the O-C-N chain are potentially reactive, amides become versatile organic compounds. This is primarily due to the delocalization of the π electrons along the O-C-N chain. Hence the ground-state structure of amide is a hybrid of the two resonance forms (1.6a) and (1.6b). Although versatility often means complexity, simplification here can be achieved by recognizing that the majority of reactions of amides fall into two classes. The first involves nucleophilic attack by the oxygen atom, or occasionally by the nitrogen atom, on either positively charged or neutral electrophilic reagents. Here the resonance form (1.6b) is usually the more appropriate reactive species. The second, and less common process involves nucleophilic addition to the amide carbonyl group of (1.6a). Most other reactions of amides such as dehydration, elimination, deamination, etc., are sequential to these two processes.

(1.6a) (1.6b)

Because of π electron delocalization along the O-C-N chain, the electrophilic properties of the carbonyl carbon atom are attenuated. Hence amides are much less reactive electrophiles than carboxylic esters. Enhancement of polarization of the C=O bond, either by protonation or complexation of the oxygen atom, is usually necessary before such a reaction can occur. Since amides are relatively weak bases, with protonation and complexation occuring on oxygen, they should also be feeble nucleophiles with oxygen being the most nucleophilic site. This explains why neutral amides react only with the more powerful electrophilic reagents forming, initially, the O-substituted derivative. Although N-substituted compounds are commonly isolated from reaction mixtures, they usually originate from rearrangements of the O-substituted derivatives and therefore represent the thermodynamically stable product [70MI1] (for further details see chapter 5). Direct N-substitution occurs only in special circumstances, either when powerful electrophilic species such as diazoalkanes are used or when the reaction is carried out in the presence of a strong base, which creates the amide conjugate base as the reactive species. For example, N-alkylation is conveniently achieved by treating a lactam successively with sodium hydride and alkyl halide in benzene.

Amides usually get hydrolyzed with N-acyl bond fission to regenerate the parent carboxylic acid and an amine.

Since the initial step requires nucleophilic addition to the carbonyl group and with amines particularly amine anions, being poor leaving groups, it is not surprising that this reaction is often sluggish. Water itself, for example, is virtually inert and many amides can be recrystallized from this solvent. Hydrolysis is much easier either under alkaline conditions, where the more powerful HO^- nucleophile is available, or under acidic conditions, where the protonation of the substrate assists both nucleophilic attack by H_2O and expulsion of the amine. Hydrolysis of lactams is similar, but is generally easier because of ring strain. However, the vinylogous amide, 4-pyridone, is quite stable under the acidic or basic conditions normally used for the hydrolysis of amides [74MI1].

1.4. Scope of the Work

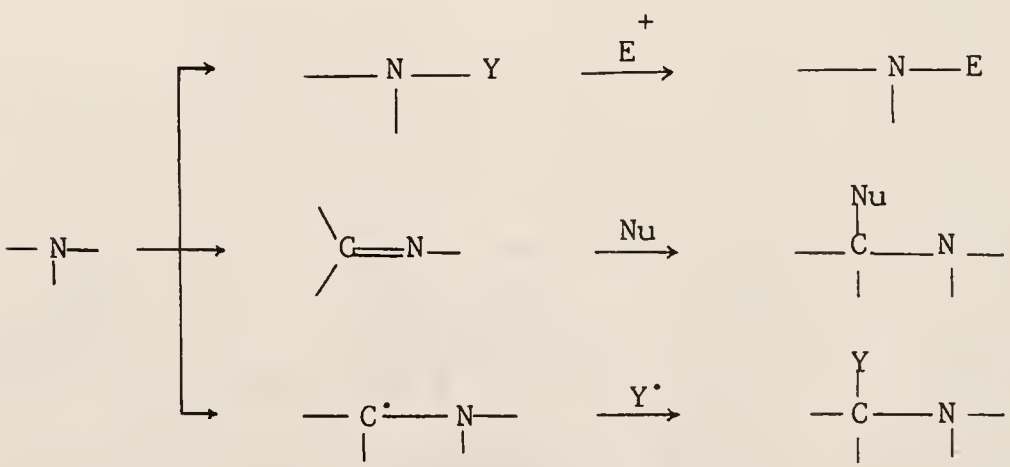
The main objectives of this work were (i) to investigate the synergistic effect of amide functionality on the α-metallation of amides, (ii) to study the conformational behavior (equilibria and kinetics) of bis- and tris-amides using NMR spectroscopy, (iii) to elucidate the mechanism of the rearrangement of an imidate to an amide in a vinylogous amide, and (iv) to study the base catalyzed hydrogen deuterium exchange behavior of different O- and N-substituted vinylogous amides.

CHAPTER 2

METALLATION OF AMIDES

2.1. Introduction

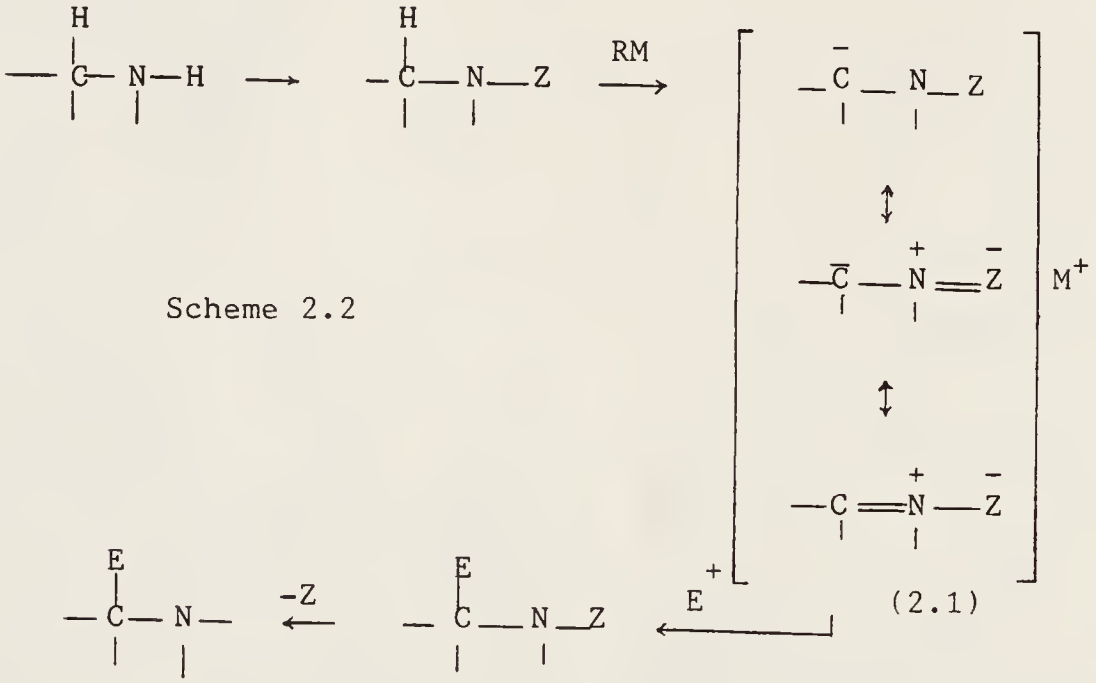
The main aim of the metallation studies on amides was for the transformation of amines into α-substituted amines. Therefore, before discussing the objective of this work a brief discussion is given on the different methods available for amine transformation. The classical methods for the preparation and transformation of amines employ (i) nucleophilic substitution by nitrogen, (ii) nucleophilic addition to a carbon nitrogen double bond and (iii) radical substitution at carbon adjacent to nitrogen (scheme 2.1).



Scheme 2.1

Recent methods however, involve introducing an activating group on the nitrogen atom and then removing the proton from the carbon adjacent to the nitrogen using metal

alkyls, to generate α-metallo amine synthetic equivalents. Then addition of an electrophile followed by the removal of activating group gives the α-electrophile substituted amine (scheme 2.2).



Scheme 2.2

(2.1)

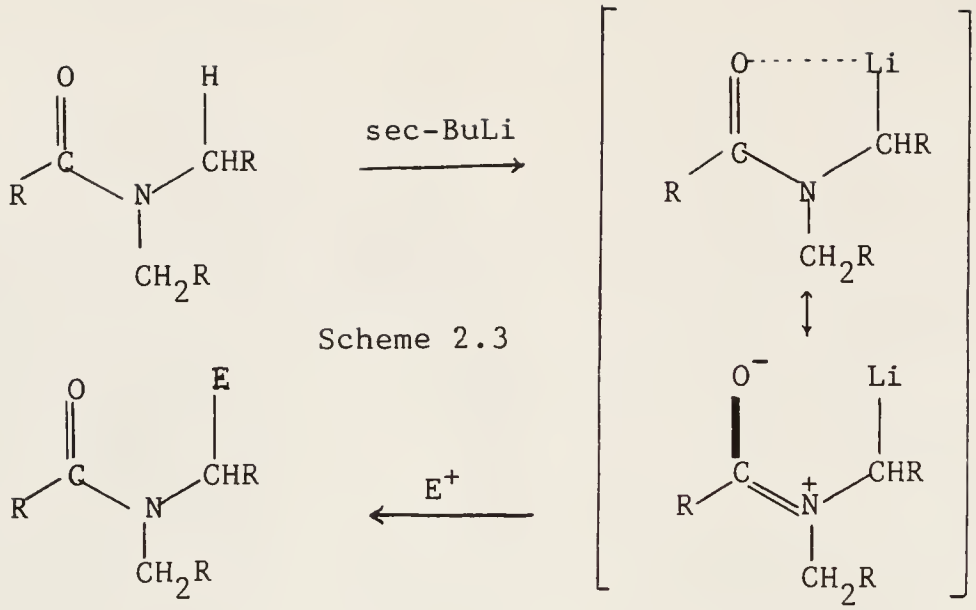
A number of species have been used as activating groups. In a recent review [84CR471] the different groups used for this transformation have been discussed, it also compares the advantages and disadvantages of the different groups which arise either from the initial introduction of the group or removal after the transformation. In all the groups discussed the main idea behind the activation was their ability to stabilize an α-carbanion by dipole stabilization.

2.1.1. Dipole Stabilized Carbanions

A carbanion is considered to be dipole stabilized when it is adjacent to a heteroatom which is the positive end of a dipole (Scheme 2.2). The group Z can provide stabilization in the transition state leading to (2.1) by complexation with the metal of the base, by dipole stabilization, and/or by resonance delocalization [84CR471]. Mechanism of metalation has been reviewed [84CR471]. In addition to dipole stabilization in the lithiation of amides by IR observation in a stopped-flow spectrometer and syn substitution indicate, complexation plays a major role in the reaction (see (2.2) of Scheme 2.3).

2.1.2. Carboxamido Group Stabilized Carbanions

The observation that dipole stabilized carbanions (2.2) can be formed from amides and undergo electrophilic substitution as shown in scheme 2.3 led to investigations of a number of systems in which the activating function Z contains a carbonyl group [78CR275, 79AG(E)239, 81JOC4108]. The carbonyl group should be efficiently added to and cleaved from the amine, as well as being resistant to nucleophilic addition by the alkyl lithium base which is required to form the carbanionic intermediate (2.2).



Scheme 2.3

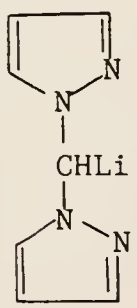
(2.2)

Various substituents adjacent to the carbonyl have been investigated in different amides and the 1,1-diethylpropyl group was found to be the best of all those considered [81JOC4316].

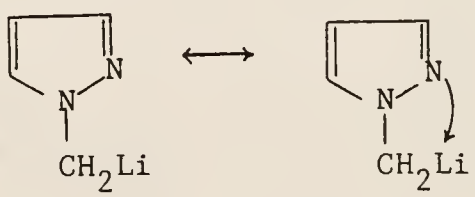
Alhough a great number of acyl groups have been used in the transformation of amines into α-substituted amines, there has been no investigation of whether there is synergistic effect, with two or more amide functionalities, on the stabilization of a carbanion.

2.1.3. Synergistic Effects in Stabilization

Dipole stabilized anions of type $RR'C^{-}NR"-X=Y$ are known for a wide variety of groups X=Y [77TL1839,78CR275]. However, little is known about the synergistic effect of such stabilization in derivatives of type $RC^{-}(NR'-X=Y)_2$. Recently, it has been demonstrated [83T4133] that lithiation of methylenebispyrazoles, to give metallated derivatives of type (2.3), is indeed somewhat easier than the formation of the corresponding monocyclic analogues (2.4).



(2.3)



(2.4a) (2.4b)

The classic example of the synergistic effect has been the work on cyclohexane-1,3-dithiane which has been greatly exploited in organic synthesis [74JAM1807, 77JAM8262, 65AG(E)1075, 65AG(E)1077, 75JOC231].

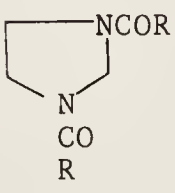
2.1.4. Aim of the Work

The aim was to study the α-metallation behavior of a series of compounds containing the structural feature $CH_2(NRCOR')_2$.

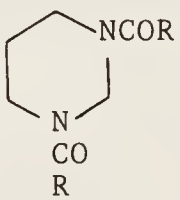
2.2. Results and Discussion

Cyclic 1,3-diamines and 1,3,5-triamines were chosen as the starting compounds and the acyl derivatives of these compounds were prepared for the study. The acyl unit was either a benzoyl or a pivaloyl group.

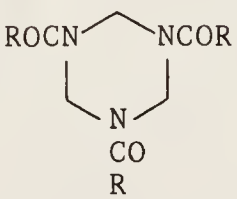
The compounds prepared for the study were - 1,3-dibenzoylimidazolidine (2.5), 1,3-dipivaloylimidazolidine (2.6), 1,3-dibenzoylhexahydropyrimidine (2.7), 1,3-dipivaloylhexahydropyrimidine (2.8), 1,3,5-tribenzoylhexahydro-sym-triazine (2.9) and 1,3,5-tripivaloylhexahydro-sym-triazine (2.10).



(2.5) R = C_6H_5
(2.6) R = $C(CH_3)_3$



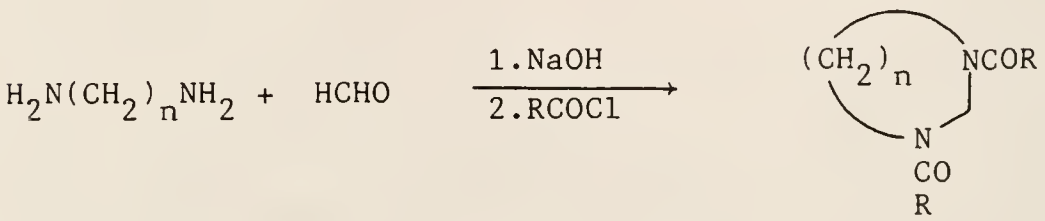
(2.7) R = C_6H_5
(2.8) R = $C(CH_3)_3$



(2.9) R = C_6H_5
(2.10) R = $C(CH_3)_3$

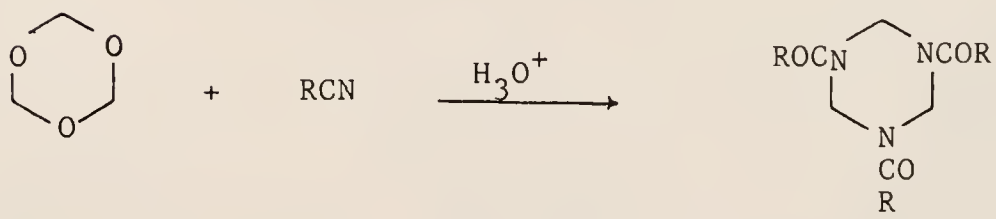
2.2.1. Preparation of Amides

Compounds (2.5) and (2.6) were prepared from 1,2-ethylene diamine, formalin and benzoyl chloride or pivaloyl chloride, respectively (scheme 2.4) . Compounds (2.7) and (2.8) were prepared from 1,3-propanediamine, formalin and benzoyl chloride or pivaloyl chloride, respectively (scheme 2.4). However, compounds (2.9) and (2.10) were prepared from sym-trioxane and benzonitrile or pivalonitrile, respectively (scheme 2.5).



(2.5) R = C_6H_5 n=2
(2.6) R = $C(CH_3)_3$ n=2
(2.7) R = C_6H_5 n=3
(2.8) R = $C(CH_3)_3$ n=3

Scheme 2.4



(2.9) R = C_6H_5
(2.10) R = $C(CH_3)_3$

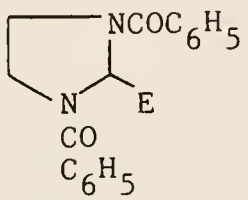
Scheme 2.5

2.2.2. Lithiation of 1,3-Diacylimidazolidines

Lithiation of (2.5) with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78°C gave a dark brown solution of a carbanion. Under most conditions, the very reactive carbanion reacted with more of (2.5) acting as an electrophile, to give the self condensation product (2.11). Formation of (2.11) was also confirmed by the appearance of a ketone carbonyl signal in the ^{13}C NMR. Addition of LDA to a mixture of (2.5) and an electrophile in THF still gave (2.11). Use of benzaldehyde or para-tolualdehyde as the electrophile gave the corresponding benzyl alcohol, along with starting material, as observed from ^{1}H and ^{13}C NMR spectra, and dimers of compound (2.5) as observed from mass spectrometry.

The use of amide (2.6) was an attempt to avoid self condensation by the introduction of steric crowding around the carbonyl group. However, this method failed as (2.6) did not react with LDA, even at 0°C. Evidently the tert-butyl group increased the steric crowding not only around the carbonyl but also around the C-2 carbon, thus hindering the approach of the base LDA to the C-2 hydrogen. Similar explanations have also been given for 1,4-dibenzoyl-2,3-dimethylquinoxalines not reacting with LDA [84JCS(P1)1949].

Use of less nucleophilic tert-butyllithium for deprotonation instead of LDA gave the expected product after treatment with an electrophile. By this procedure the C-2 methylated compound (2.12) was obtained from compound (2.5) using methyl iodide as the electrophile. However, the expected product was not isolated with compound (2.6) and methyl iodide.



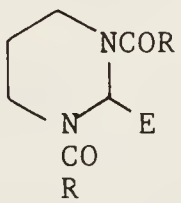
(2.11) E = COC_6H_5

(2.12) E = CH_3

2.2.3. Lithiation of 1,3-Diacylhexahydropyrimidines

Lithiation of (2.7) with LDA also afforded a dark colored solution indicating the formation of the carbanion, but again on work-up only the self condensation product (2.13) was obtained. The same product (2.13) was also obtained on adding LDA to a solution of (2.7) and an electrophile in THF. When benzaldehyde or para-tolualdehyde was used as the electrophile, the corresponding benzyl alcohol was formed, as evidenced by ^1H and ^{13}C NMR. Use of tert-butyllithium as the base with compound (2.7) gave the expected carbanion which was trapped with D_2O to give (2.14).

A more stable carbanion was obtained from (2.8) in THF at -78°C with LDA, and this was trapped with D_2O to give (2.15), and with methyl iodide to give (2.16). The ^1H NMR spectrum of (2.15) showed four signals with chemical shifts identical to the starting material (2.8), however, the intensity of the signal for the C-2 proton was one fourth of the signal for the C-4 and C-6 protons.



(2.13) R = C_6H_5 E = COC_6H_5

(2.14) R = C_6H_5 E = D

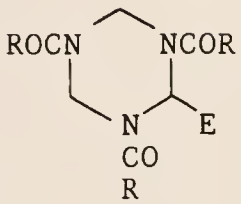
(2.15) R = $C(CH_3)_3$ E = D

(2.16) R = $C(CH_3)_3$ E = CH_3

2.2.4. Metallation of 1,3,5-Triacylhexahydro-sym-triazines

Low solubility of (2.9) in THF and DME below 0°C prevented the usual procedure with LDA as base. However, LDA addition at 25°C gave the carbanion which was trapped with D_2O to give (2.17). Metallation under polar conditions was attempted, but treatment of (2.9) with dimsyl sodium followed by an electrophile gave only starting material back.

Lithiation of (2.10) in THF at -78°C with LDA gave the carbanion, which was trapped with D_2O to give (2.18).



(2.17) R = C_6H_5 E = D

(2.18) R = $C(CH_3)_3$ E = D

2.3. Conclusions

Lithiation studies with 1,3-diacylimidazolidines, 1,3-diacylhexahydropyrimidines and 1,3,5-triacylhexahydro-sym-triazines (Table 2.1) indicate that no substantial additional increase in carbanion stability occurs as a result of the introduction of the second dipolar stabilizing group. This might be due to the fact that the conformer favoring the double stabilization was not the predominant conformer (discussed in chapter 3). Within the amides studied the carbanions derived from the benzoyl derivatives (2.5), (2.7) and (2.9) were found to be less stable, with (2.5) being the least. However, carbanions derived from pivaloyl derivatives (2.8) and (2.10) were found to be more stable with (2.8) being the most. This might have been due to the increase in steric crowding around the amide C=O bonds, making them less susceptible for nucleophilic

Table 2.1 Formation of α-Lithio Species of Amides and their Reaction with Electrophiles

Amide	Procedure[a]	Electrophile	Product	Yield (%)
(2.5)	A	-	(2.11)[b]	90
(2.5)	B	CH_3I	(2.12)	20
(2.7)	A	-	(2.13)[b]	80
(2.7)	B	D_2O	(2.14)	20
(2.8)	A	D_2O	(2.15)	50
(2.8)	A	CH_3I	(2.16)	80
(2.9)	A	D_2O	(2.17)	65
(2.10)	A	D_2O	(2.18)	85

a For a description of General Procedure A and B see Experimental.

b The same product was also obtained in presence of electrophiles.

addition reactions. In addition, ring size was also found to be a factor. Five-membered ring was found to be more influenced by the steric nature of the acyl unit than the six-membered.

2.4. Experimental

Melting points were recorded on a Bristoline hot-stage microscope and were uncorrected. Proton NMR spectra were recorded on a Varian EM 360L spectrometer using internal Me_4Si as the reference. IR spectra were obtained on a Perkin-Elmer 283 B spectrophotometer.

2.4.1. Reagents

Tetrahydrofuran (THF) was refluxed over and distilled from sodium benzophenone ketyl. n-BuLi (1.6 M in hexane) and t-BuLi (1.7 M in pentane) were standardised by titration [80CC87]. Diisopropylamine was refluxed over and distilled from CaH_2.

2.4.2. Preparation of Acyl Derivatives of Imidazolidines, Hexahydropyrimidines and Hexahydro-sym-triazines

Preparation of 1,3-dibenzoylimidazolidine (2.5):

Ethylenediamine (5 g, 0.08 M) and formaldehyde (6 g, 37% solution) at 100°C were stirred for 0.5 h. The viscous

colorless liquid was then kept at 55-60°C. Benzoyl chloride (20 g, 0.14 M) was added dropwise over 30 min. while maintaining a pH of 8-10 with 10% NaOH solution (75 mL). The mixture was then stirred for 1 h at 25°C. The 1,3-dibenzoylimidazolidine separated out and was recrystallized from acetone (10 g, 40%) as plates, m.p. 140°C (lit.[73JHC439], m.p. 140-141°C); ν_{max} ($CHBr_3$) 1628 cm^{-1}; δ ($CDCl_3$) 3.88 (4 H, s), 5.19 (2 H, s), and 7.55 (10 H, s).

Preparation of 1,3-dipivaloylimidazolidine (2.6):

Ethylenediamine (5 g, 0.08 M), formaldehyde (6 g, 37% solution) and water (50 mL) were stirred at 100°C for 1 h. To the viscous colorless liquid, aqueous sodium hydroxide (32 g, 0.8 M in 120 mL of water) was added. The mixture was cooled to between -10 and -20°C and trimethylacetyl chloride (19.2 g, 0.16 M) added dropwise. After further stirring for 1 h, 1,3-dipivaloylimidazolidine (9 g, 50%), separated. The crude solid was washed with water and recrystallized from chloroform, to give prisms, m.p. 141°C (Found: C, 64.7; H, 10.1; N, 11.4. $C_{13}H_{24}N_2O_2$ requires C, 64.9; H, 10.1; N, 11.6%); ν_{max}($CHBr_3$) 1620 cm^{-1}; δ ($CDCl_3$) 1.28 (18 H, s), 3.79 (4 H, s), and 5.05 (2 H, s).

Preparation of 1,3-dibenzoylhexahydropyrimidine (2.7):

Propane-1,3-diamine (15 g, 0.20 M), water (150 mL) and formaldehyde (37%, 25 mL) were stirred at 100°C for 2 h. Sodium hydroxide (2.5 M, 75 mL) was added at 25°C and then

benzoyl chloride (28 g, 0.20 M) dropwise. After stirring for another 1 h, 1,3-dibenzoylhexahydropyrimidine (15 g, 25%) separated. Crystallization from ether-chloroform gave plates, m.p. 94-95°C (lit.[67AJC1643], m.p. 92-96°C); ν_{max} ($CHBr_3$)1625 cm^{-1}; δ ($CDCl_3$) 1.80 (2 H, m), 3.81 (4 H, t, J=6 Hz), 5.17 (2 H, s) and 7.40 (10 H, s).

Preparation of 1,3-dipivaloylhexahydropyrimidine (2.8):

Propane-1,3-diamine (3.7 g, 0.05 M), formaldehyde (37% 25 mL) and water (150 mL) were stirred at 100°C for 2h. Sodium hydroxide (2.5 M, 70 mL) was added at -40°C, and then pivaloyl chloride (12.1 g, 0.10 M) was added dropwise. After stirring the mixture at 0°C for 1 h, column chromtography (alumina and ether) gave 1,3-dipivaloylhexahydropyrimidine (4 g, 32%) which crystallized as plates (from ether), m.p. 115°C (Found: C, 65.9; H, 10.0; N, 11.3. $C_{14}H_{26}N_2O_2$ requires C, 66.1; H, 10.3; N, 11.0%); ν_{max} ($CHBr_3$) 1620 cm^{-1}; δ ($CDCl_3$) 1.28 (18 H, s), 1.70 (2 H, m), 3.76 (4 H, t, J=6 Hz) and 5.31 (2 H, s).

Preparation of 1,3,5-tribenzoylhexahydro-sym-triazine (2.9):

Compound (2.9) was prepared as reported earlier [76S467], it formed prisms from ether-chloroform, m.p. 221°C (lit. [76S467], m.p. 220-223°C); ν_{max} ($CHBr_3$) 1640 cm^{-1}; δ ($CDCl_3$) 5.30 (6 H, s), 7.40 (15 H, s).

Preparation of 1,3,5-tripivaloylhexahydro-sym-triazine (2.10):

Compound (2.10) was prepared following the literature method [76S467] for (2.9) in 45% yield as needles from ether-chloroform, m.p. 134-136°C (Found: C, 63.8; H, 9.9; N, 12.2. $C_{18}H_{33}N_3O_3$ requires C, 63.7; H, 9.7; N, 12.3 %); $\nu_{max}(CHBr_3)$ 1630 cm^{-1}; δ ($CDCl_3$) 1.35 (27 H, s) and 5.40 (6 H, s).

2.4.3. Lithiation of the Acyl Derivatives of Imidazolidines, Hexahydropyrimidines and Hexahydro-sym-triazines

General procedure A:

LDA (1 mmol) was prepared by adding dropwise di-isopropylamine (0.14 mL, 1 mmol) to n-butyllithium in hexane (1 mmol) at -20°C under nitrogen. Stirring was continued until it became cloudy (0.5 h) and then dry THF (5 mL) was added. The mixture was then cooled to -78°C and the amide (1 mmol) in dry THF (10 mL) was added. Stirring was continued for 1 h at -78°C and for 10 h more at 20°C. Water (1 mL) was added, and solvents removed at 40-50°C/20 mmHg. The residue in methylene chloride (50 mL) was washed with saturated aqueous NaCl (10 mL) and water (10 mL) and then dried (sodium sulphate) and evaporated at 40-50°C/20 mmHg. Products were separated by column chromatography.

General procedure B:

Similar to procedure A except that t-butyllithium was used instead of LDA.

2.4.4. Lithiation of 1,3-Dibenzoylimidazolidine

1,3-Dibenzoyl-2-methylimidazolidine (2.12):

Following procedure B using 1,3-dibenzoylimidazolidine (2.5) with methyl iodide as the electrophile gave 1,3-dibenzoyl-2-methylimidazolidine (2.12) (20%) as needles from $CHCl_3$, m.p. 150°C (Found: C, 73.3; H, 6.3; N, 9.4. $C_{18}H_{18}N_2O_2$ requires C, 73.5; H, 6.1; N, 9.5 %); ν_{max}($CHBr_3$) 1625 cm^{-1}; δ ($CDCl_3$) 8.30-7.30 (10 H, m), 5.50 (1 H, q, J=5 Hz), 4.35-3.60 (4 H, m) and 1.38 (3 H, d, J=5 Hz).

1,2,3-Tribenzoylimidazolidine (2.11):

1,3-Dibenzoylimidazolidine (2.5) following procedure A self condensed to give 1,2,3-tribenzoylimidazolidine (2.11) (90%) as needles from $CHCl_3$, m.p. 228°C (Found: C, 74.8, H, 5.5; N, 7.4. $C_{24}H_{20}N_2O_3$ requires C, 75.0; H, 5.2; N, 7.3 %); ν_{max} ($CHBr_3$) 1710, 1625 cm^{-1}; δ ($CDCl_3$) 8.50-7.30 (15 H, m), 4.00 (4 H, s) and C-2 proton not observed.

2.4.5. Lithiation of 1,3-Dibenzoylhexahydropyrimidine

2-Deuterio-1,3-dibenzoylhexahydropyrimidine (2.14):

1,3-Dibenzoyl-hexahydropyrimidine (2.7) following procedure B with D_2O as the electrophile gave 2-deuterio-1,3-dibenzoylhexahydropyrimidine (2.14) (20%) as needles from ether, m.p. 95°C (Found: C, 73.2; H, 5.8; N, 9.1. $C_{18}H_{17}DN_2O_2$ requires C, 73.2; H, 5.8; N, 9.5); ν_{max} $(CHBr)_3$ 1625 cm^{-1}; δ ($CDCl_3$) 7.40 (10 H, s), 5.17 (1 H, s), 3.81 (4 H, t J=6 Hz), and 1.80 (2 H, m).

1,2,3-Tribenzoylhexahydropyrimidine (2.13):

1,3-Dibenzoylhexahydropyrimidine (2.7) following procedure A without any electrophile gave 1,2,3-tribenzoylhexahydropyrimidine (2.13) (80%) as needles from $CHCl_3$, m.p. 225°C (Found: C, 75.2; H, 5.7; N, 7.0. $C_{25}H_{22}N_2O_3$ requires C, 75.4; H, 5.5; N, 7.0 %); ν_{max} ($CHBr_3$) 1715, 1628 cm^{-1}; δ ($CDCl_3$) 8.20-7.25 (15 H, m), 4.05-3.30 (4 H, m), 1.90-1.30 (2 H, m) and C-2 proton not observed.

2.4.6. Lithiation of 1,3-Dipivaloylhexahydropyrimidine

2-Deuterio-1,3-dipivaloylhexahydropyrimidine (2.15):

1,3-Dipivaloylhexahydropyrimidine (2.8) following procedure A with D_2O as electrophile gave 2-deuterio-1,3-dipivaloylhexahydropyrimidine (2.15) (50%) as plates from

CH_2Cl_2, m.p. 115-116°C (Found: C, 65.8; H, 10.1; N, 10.8. $C_{14}H_{25}DN_2O_2$ requires C, 65.9; H, 9.8; N, 11.0 %); ν_{max} ($CHBr_3$) 1620 cm^{-1}; δ ($CDCl_3$) 5.25 (1 H, s), 3.75 (4 H, t, J=6 Hz), 1.67 (2 H, m) and 1.26 (18 H, s).

1,3-Dipivaloyl-2-methylhexahydropyrimidine (2.16):

1,3-Dipivaloylhexahydropyrimidine (2.8) following procedure A with methyl iodide as the electrophile gave 1,3-dipivaloyl-2-methylhexahydropyrimidine (2.16) (80% based on recovery of starting material) as needles from $CHCl_3$, m.p. 125°C (Found: C, 67.5; H, 10.6; N, 10.3. $C_{15}H_{28}N_2O_2$ requires C, 67.2; H, 10.4; N, 10.4 %); ν_{max} ($CHBr_3$) 1630 cm^{-1}; δ ($CDCl_3$) 6.90 (1 H, q, J=6 Hz), 4.40-3.40 (4 H, m), 2.00-1.40 (2 H, m), 1.29 (18 H, s) and 1.18 (3 H, d, J=6 Hz).

2.4.7. Lithiation of 1,3,5-Tribenzoylhexahydro-sym-triazine

2-Deuterio-1,3,5-tribenzoylhexahydro-sym-triazine (2.17):

1,3,5-Tribenzoyl-hexahydro-sym-triazine (2.9) following procedure A, but with addition of LDA to (2.9) in THF at 25°C, with D_2O as the electrophile gave 2-deuterio-1,3,5-tribenzoylhexahydro-sym-triazine (2.17) (65%) as plates from $CHCl_3$, m.p. 221°C (Found: C, 72.1; H, 5.3; N, 10.3. $C_{24}H_{20}DN_3O_3$ requires C, 72.0; H, 5.0; N, 10.5 %); ν_{max}($CHBr_3$) 1640 cm^{-1}; δ ($CDCl_3$) 7.54 (15 H, s) and 5.40 (5 H, s).

2.4.8. Lithiation of 1,3,5-Tripivaloylhexahydro-sym-triazine

2-Deuterio-1,3,5-tripivaloylhexahydro-sym-triazine (2.18):

1,3,5-Tripivaloylhexahydro-sym-triazine (2.10) following procedure A with D_2O as the electrophile gave 2-deuterio-1,3,5-tripivaloylhexahydro-sym-triazine (2.18) (85%) as plates from $CHCl_3$, m.p. 135°C (Found: C, 63.4; H, 9.6; N, 12.2. $C_{18}H_{32}DN_3O_3$ requires C, 63.5; H, 9.4; N, 12.3 %); $\nu_{max}(CHBr_3)$ 1630 cm^{-1}; δ ($CDCl_3$) 5.40 (5 H, s) and 1.35 (27 H, s).

CHAPTER 3

CONFORMATIONAL ANALYSIS OF AMIDES

3.1. Introduction

During the last two decades, NMR spectroscopy has developed into one of the most valuable techniques for investigating molecular structure and stereochemistry. Not only can NMR give the extent of equilibrium between different conformers but can also yield information about the dynamic behavior of the different conformers at various temperatures. This is referred to as dynamic nuclear magnetic resonance (DNMR). The barrier heights or the free energy of activation of dynamic processes amenable to this technique conveniently extend just from the border line of 20-25 kcal $mole^{-1}$, below which compounds become too unstable to be isolated, to about 5-6 kcal $mole^{-1}$. Restricted rotation about the C(O)-N bond in amides is the classical example of a rate process that can be studied by DNMR.

Activation parameters can be obtained to a greater accuracy using total line shape analysis. However, a great number of references are available indicating that the

coalescence temperature has been used to obtain the free energy of activation.

3.1.1. Conformational Analysis Using DNMR

Though DNMR has been used to study all types of compounds like substituted ethanes, amides, carbamates, thioamides, nitrosoamines, nitriles, aldehydes and ketones, only amides will be discussed here.

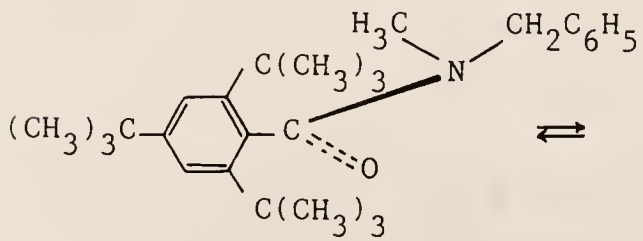
Resonance theory describes the electronic structure of amides as a hybrid of (3.1a) and (3.1b) suggesting a certain amount of double-bond character for the C(O)-N bond, and thus there is a concomitant increase of the rotational barrier over that in pure single bonds. There is a chance to observe the rate process by DNMR because R' and R" reside in different magnetic environments (R' being more shielded than R") [63JAM3728] in the fixed structure (3.1) but are time-averaged on rapid rotation. This prediction was first confirmed for dimethylformamide and dimethylacetamide [55JCP1363].

(3.1a) (3.1b)

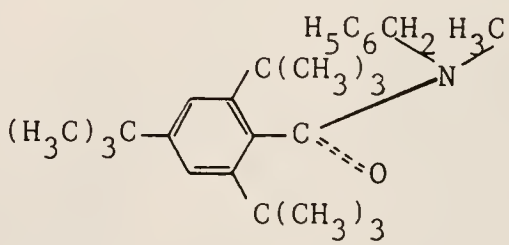
3.1.2. DNMR Studies on Monoamides

Of the total number of DNMR studies done on amides, the major portion has been on monoamides. Initial studies on dimethylformamide from different groups showed barriers from 6.3-28.2 kcal $mole^{-1}$, which was later attributed to factors like solvent, concentration, temperature and long range coupling in addition to instrumental errors. However, using high field and high resolution instruments with specified solvent and specified concentration, the difficulties are overcome. For determination of an accurate value for the free energy of activation, the total line shape analysis method has always been used.

A great deal of work has been done on the effect of substituents (both on the nitrogen and on the carbonyl group), solvent, and concentration on the barrier. In certain cases stable amide conformers have been isolated in pure form [66TL4593], such as in the case of (3.2) where a severe steric interaction raises the barrier by an additional amount (30-32 kcal $mole^{-1}$).



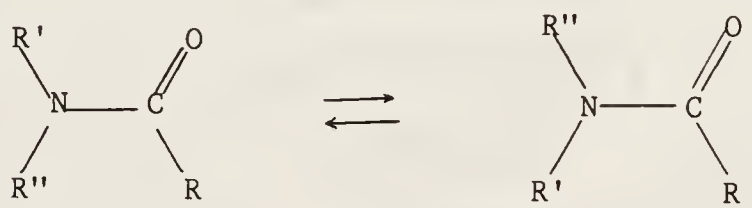
(3.2a)



(3.2b)

3.1.3. DNMR Studies on Polyamides

Restriction of rotation about the C(O)-N bond of amides has been the subject of intensive study, and the structural influences on the equilibria and kinetics of the syn-anti interconversion are well understood for monoamides (scheme 3.1) [68MI1]. However, the same wealth of information is not available for polyamides. Conformational properties of polyamides have been obtained from NMR studies of the conformation of model diamides derived from trans-1,2-cyclohexane carboxylic acid and different aliphatic amines [72MM197], and piperazine or N,N'-dimethylethylenediamine and aliphatic or aromatic carboxylic acids [69MM154]. Signals for the different conformational isomers in diamides have been assigned using paramagnetic shifts induced by $Eu(fod)_3$ complexes [72JOC3434].



Scheme 3.1

Indeed, the investigation of DNMR spectra involving more than two different species has been relatively limited. NMR investigation of thiophene-2,5-dicarboxaldehyde has been done in liquid crystals [72JCS(P2)755]. Rotational isomerism of N,N'-dimethyl-α,ω-bis(benzoylamino)alkanes [84JCS(P2)1089] and 1,3,5-trinitrosohexahydro-1,3,5-triazine [69RC1687] has been studied using variable temperature ^{1}H NMR spectroscopy. Stereoisomerization of N,N'-diacetyl-N,N'-dimethylhydrazine using variable temperature ^{1}H NMR spectroscopy has also been studied and a discussion about the mechanism of stereoisomerisation was given [75GCI569].

3.1.4. Aims of the work

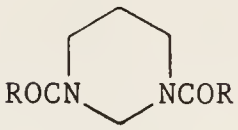
The goals of this work were (i) to elucidate the equilibria on some cyclic model systems of bis- and tris-amides, (ii) to calculate the rotational barriers and (iii) to deduce the mechanism of rotation based on the spectral behavior at various temperatures.

3.2. Results and Discussion

The model systems chosen for the bis-amide studies were 1,3-diacylimidazolidines (3.3) and (3.4) and 1,3-diacylhexahydropyrimidines (3.5) and (3.6). For the tris-amide studies it was 1,3,5-triacylhexahydro-sym-triazines (3.7) and (3.8).

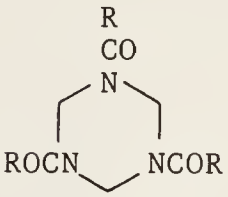
(3.3) R = C_6H_5

(3.4) R = $C(CH_3)_3$



(3.5) R = C_6H_5

(3.6) R = $C(CH_3)_3$



(3.7) R = C_6H_5

(3.8) R = $C(CH_3)_3$

3.2.1. Conformers of Diamides and Triamides

A single amide bond can exhibit two conformations. Similarly two amide bonds together can exhibit four conformations and three amide bonds together can exhibit eight conformations. However, on deriving these amides by acylating cyclic di- and triamines (keeping the acyl groups the same) some of the conformers become indistinguishable. For example, in compounds (3.3), (3.4) (3.5) and (3.6) although there are four possible conformers only three are distinguishable. Furthermore, for compounds (3.7) and (3.8) of the eight possible conformers, only two of them are distinguishable. The indistinguishable conformers are referred to as topomers [71].

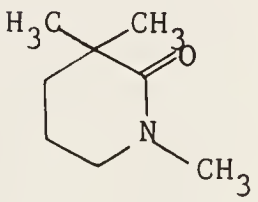
Distinguishing the different conformers experimentally (in this case using NMR) was not an easy task. To diagnose this, model compounds were developed to assign chemical shifts to the different conformations of the compounds (3.3-3.8).

3.2.2. Model Compounds for Conformational Analysis of Acyl Derivatives of Cyclic Secondary Amines - Imidazolidine, Hexahydropyrimidine and Hexahydro-sym-triazine

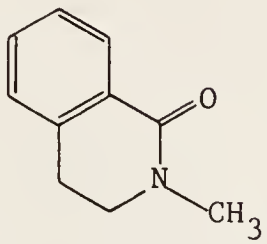
On investigating the different conformers of all the compounds, the methylene group between the two nitrogen atoms was found to be either between the two carbonyl oxygens, or between the R groups of the acyl units or between one carbonyl oxygen and one R group of the acyl unit. Although it was known already that the N-alkyl group syn to the carbonyl is always more shielded than when it is anti [63JAM3728], model compounds were still used for the signal assignments.

Since pivaloyl and benzoyl derivatives of amines were used, comparison was done with similar model systems. 1,3,3-Trimethyl-2-piperidone (3.9) showed the N-methyl (necessarily syn to the carbonyl) at delta 3.00 ppm

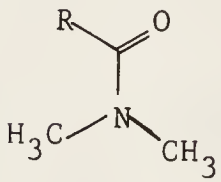
[75CJC1682]. By analogy, the syn-methyl in N,N-dimethylpivalamide (3.10) has been assigned to the signal at 2.96 ppm and the anti-methyl to the signal at 3.21 ppm in the ^1H NMR spectrum obtained at -40°C.



(3.9)



(3.11)



(3.10) R = $C(CH_3)_3$

(3.12) R = C_6H_5

(3.13) R = H

(3.14) R = CH_3

In the phenyl series, the model compound N-methyl-1,2,3,4-tetrahydro-2-isoquinolone (3.11) showed the (necessarily syn) N-CH_3 signal at delta 3.20 ppm [82T539]. N,N-Dimethylbenzamide (3.12) at -26.6°C in CH_2Br_2 showed signals at delta 3.38 and 3.53 ppm for the N-CH_3 protons [62JPC540] and in comparison with (3.11), the signal at delta 3.38 ppm was assigned to methyl syn to the carbonyl.

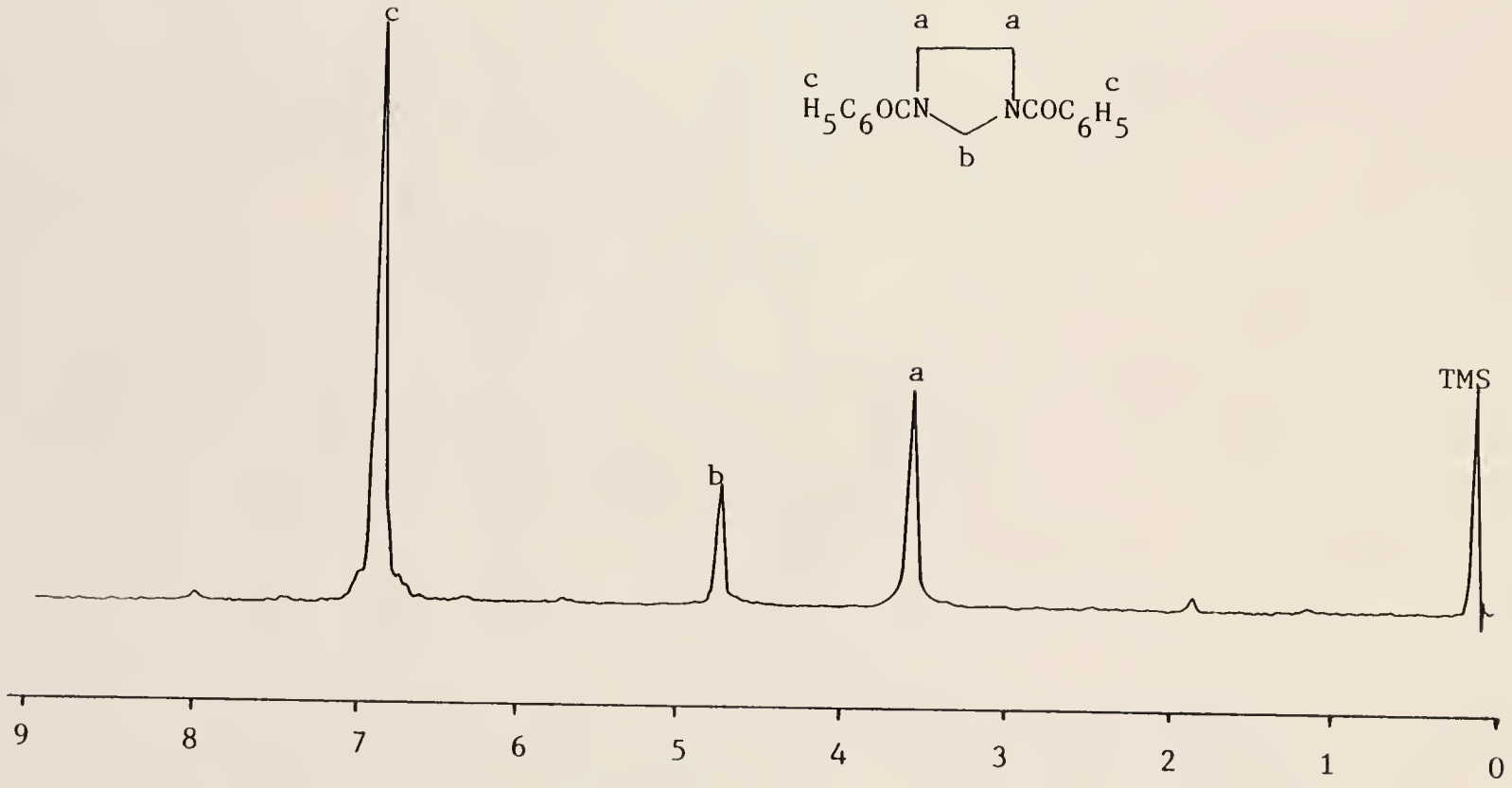


Fig. 3.1 60 MHz ^1H NMR Spectrum of 1,3-Dibenzoylimidazolidine (in $CDCl_3$) at 25°C.

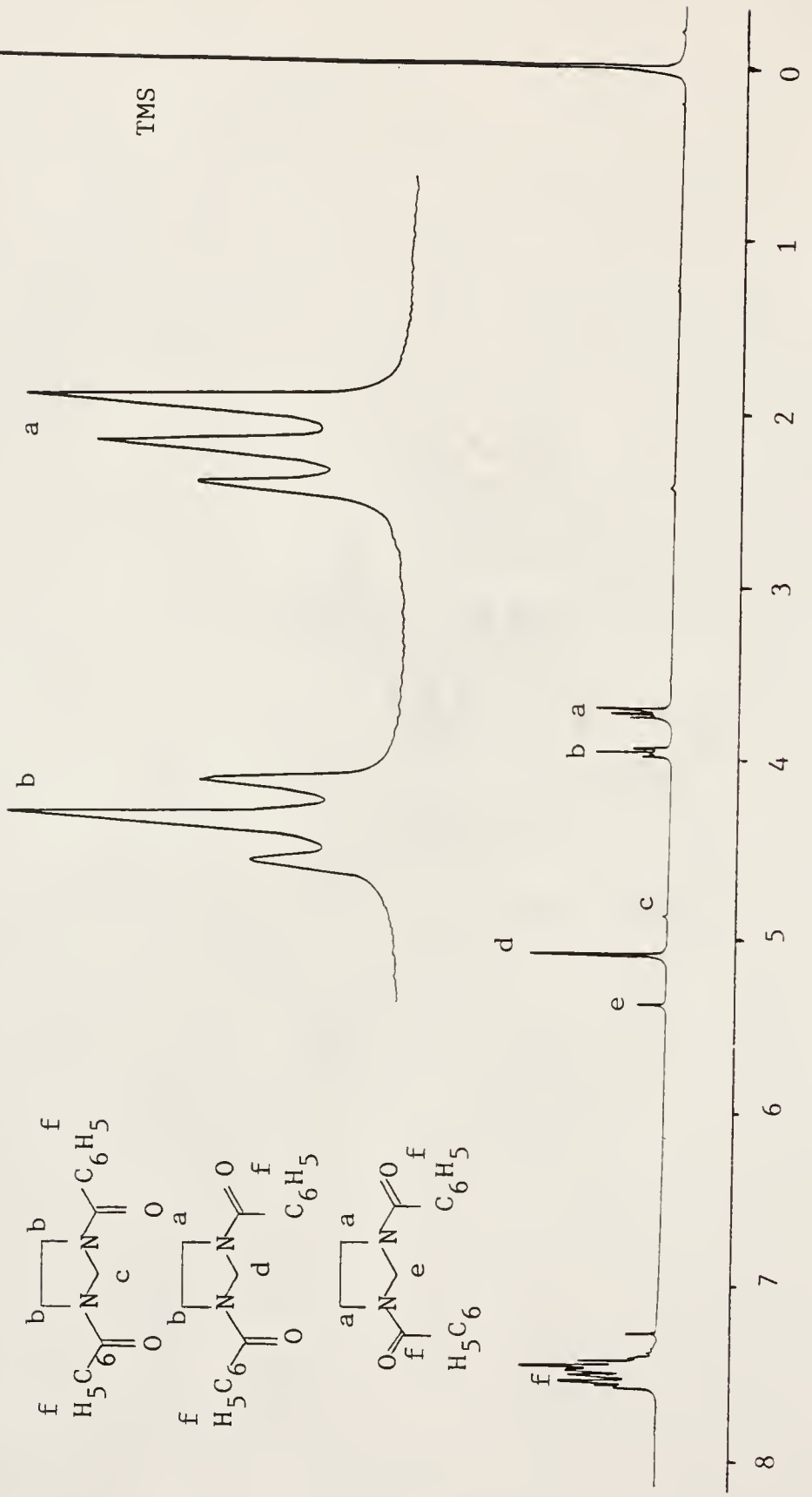


Fig. [illegible] 300 MHz ^{1}H NMR Spectrum of 1,3-Dibenzoylimidazolidine (in $CDCl_3$) at −30°C.

Fig. 3.3 60 MHz ^1H NMR Spectrum of 1,3-Dipivaloylimidazolidine (in $CDCl_3$) at 25°C.

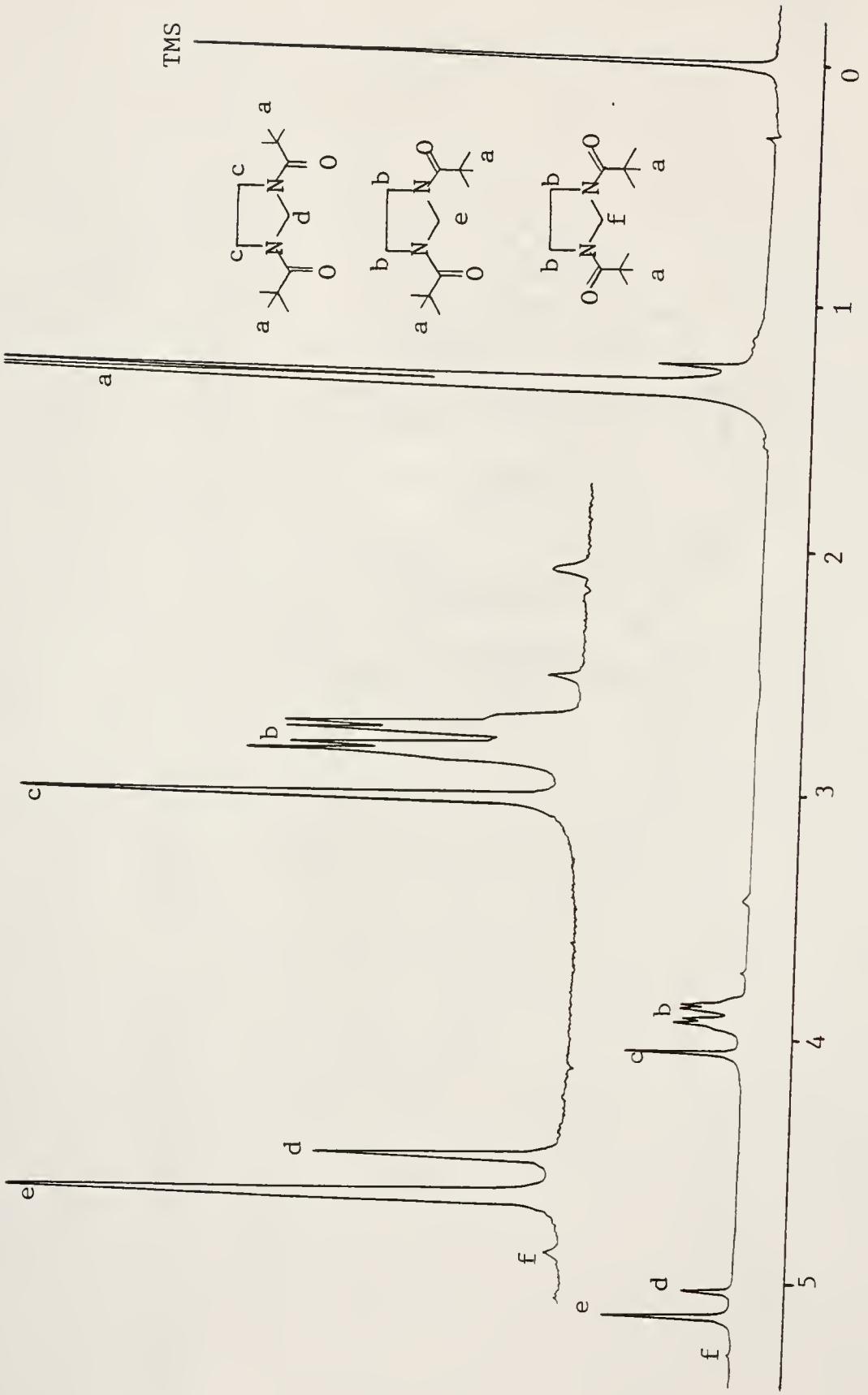


Fig. 4 300 MHz ^{1}H NMR Spectrum of 1,3-Dipivaloylimidazolidine (in $CDCl_3$) at -70°C.

In the case of ^{13}C spectra the signals were assigned to different conformers by referring to model compounds (3.13), (3.14) and particularly (3.12), in which the N-methyl carbons syn to the carbonyl group had been always shielded (31.1, 34.5, 35.2 ppm, respectively) compared to the anti N-methyl carbons (36.2, 37.5, 38.9 ppm, respectively) [78MI1]. In addition, the intensity and the number of signals were also used for the signal assignments.

An interesting feature of these results from the model systems considered both for proton and carbon, is that groups syn to the carbonyl oxygen are always shielded over the groups anti to it.

3.2.3. 1,3-Diacylimidazolidines Conformational Equilibria from ^1H NMR Spectra

At 25°C for compound (3.3) (figure 3.1) and for (3.4) (figure 3.3), a 2H singlet for 2-CH_2 and a 4H singlet for 4,5-C_2H_4 were observed, which demonstrated rapid rotation about both amide links (Table 3.1). As the temperature was lowered, these peaks broadened and split and, below -30°C for (3.3) (figure 3.2) and below -80°C for (3.4) (figure 3.4), separate signals were observed for each of the three conformers (Table 3.1). In addition to the above, (3.3) shows signals for the phenyl protons at 7.56 ppm as a broad singlet and (3.4) for the t-Bu at 1.28 ppm as a singlet. On

Table 3.1 ^{1}H NMR Chemical Shifts (ppm), J Values (Hz) and Relative Population (%) for 1,3-Diacylimidazolidines (3.3) and (3.4)

Temp.	compound	2-CH_2		popn.	4,5-C_2H_4				popn	R		
°C	(conformer)	δ	I	(%)	δ	M	J	I	(%)	δ	M	I
25[a]	(3.3)	5.20	2.00[b]	-	3.88	s	-	4.00	-	7.56	s	10.44
-30[c]	(3.3a)	4.95	0.07	3.5	4.03	s	-	0.21	5.3	7.50	m	10.54
	(3.3b)	5.17	1.60	80.0	4.03	t	7	3.18	79.5			
					3.82	t	7					
	(3.3c)	5.45	0.33	16.5	3.79	s	-	0.61	15.2			
25[a]	(3.4)	5.15	2.00[b]	-	3.85	s	-	4.00	-	1.28	s	18.00
-70[c]	(3.4a)	5.01	0.55	27.5	4.05	s	-	1.23	30.8	1.24[d]	s	[e]
	(3.4b)	5.12	1.40	70.0	3.93	t	6	2.71	67.7	1.28[d]	s	[e]
					3.86	t	6					
	(3.4c)	5.27	0.05	2.5	3.72	s	-	0.06	1.5	1.31[d]	s	[e]

M = multiplicity; t = triplet; s = singlet; m = multiplet. J =coupling constant (Hz); I = intensity. [a] 60 MHz spectrum. [b] Intensity reference standard. For low temperature spectra, total intensity of 2.0 for these peaks taken as standard. [c] 300 MHz spectrum. [d] Tentative assignment. [e] Total intensity 18.8, individual intensities not measurable due to overlap.

cooling, these peaks broaden and reappear respectively as a multiplet near 7.50 ppm for (3.3) and as three singlets at 1.31, 1.28 and 1.24 ppm for (3.4).

Comparing the model compounds for chemical shift assignment in conformers (a), (b), and (c) (scheme 3.2) of (3.3) and (3.4), we expect the 2-CH_2 protons to be at highest field in (a) where they are syn to both carbonyls and at lowest field in (c) where they are anti to both carbonyls. Conversely, conformer (a) should show a singlet at lower field for the 4,5-C_2H_4 protons than the singlet for (c). In the unsymmetrical conformer (b), the 4,5-C_2H_4 protons should display an AA'XX' pattern, with the chemical shift for A nearer to that of conformer (c) and of X nearer to conformer (a). The assignments in Table 3.1 followed these considerations.

The relative proportions of the three conformers obtained from the relative signal intensities are also shown in Table 3.1. Those for the 2-CH_2 indicate (a):(b):(c) = 3.5:80.0:16.5% for (3.3) and (a):(b):(c) = 27.5:70.0:2.5% for (3.4). Those for the 4,5-CH_2 indicate (a):(b):(c) = 5.3:79.5:15.2% for (3.3) and (a):(b):(c) = 30.8:67.7:1.5% for (3.4). Since the 2-CH_2 signals are separate singlets

for the different conformers, they are considered to be more reliable for isomer proportion deduction than the 4,5-CH_2 signals, for which the singlet for the conformers (a) and (c) overlaps with the AA'XX' double triplets from conformer (b).

Rationalizing our results it seems that in the equilibrium for (3.3) at -30°C, conformer (b) was favored over (a) by 1.51 kcal $mole^{-1}$ and over (c) by 0.76 kcal $mole^{-1}$. However, for (3.4) at -70°C, conformer (b) was favored over (a) by 0.35 kcal $mole^{-1}$ and over (c) by 1.28 kcal $mole^{-1}$.

3.2.4. 1,3-Diacylhexahydropyrimidines Conformational Equilibria from ^1H NMR Spectra

At 25°C compounds (3.5) (figure 3.5) and (3.6) (figure 3.7), showed a 2H singlet for the 2-CH_2 protons, which demonstrates that, just as for (3.3) and (3.4), rapid rotation occurs about both amide links (Table 3.2). At low temperatures for (3.5) (figure 3.6) the peaks broaden and split and at -30°C separate signals were observed for each of the three conformers. However, for (3.6) (figure 3.8) at -103°C separate signals were seen only for two conformers.

Signal assignments were based on model compounds discussed earlier. The C_5 protons gave an additional signal around 1.9 ppm. The assignments of Table 3.2 follow these considerations. For example the assignments for the 2-CH_2 protons of (3.5) and (3.6) are as follows; at -30°C, (3.5) showed three signals for the 2-CH_2 protons. Using the rule derived from model compounds that protons syn to the carbonyl oxygen were shielded, the one to the lowest field was assigned to (3.5c), the one to the highest field to (3.5a), and the middle one to (3.5b) (scheme 3.3). On similar grounds, of the two signals observed for compound (3.6), the most intense signal was assigned to (3.6b) and the remaining one being at higher field than that of (3.6b), was assigned to (3.6a). Assignments for the C_4-C_6 protons were made similarly (Table 3.2).

Relative signal intensities and the isomer proportions from the 2-CH_2 signals are shown in Table 3.2. For (3.5), (a):(b):(c) = 39.7:53.3:7.0% and for (3.6), (a):(b):(c) = 8:92:0%. From the 4,6-CH_2 signals, it was not possible to derive conformer proportions because of additional coupling to the 5-CH_2, and overlapping of signals.

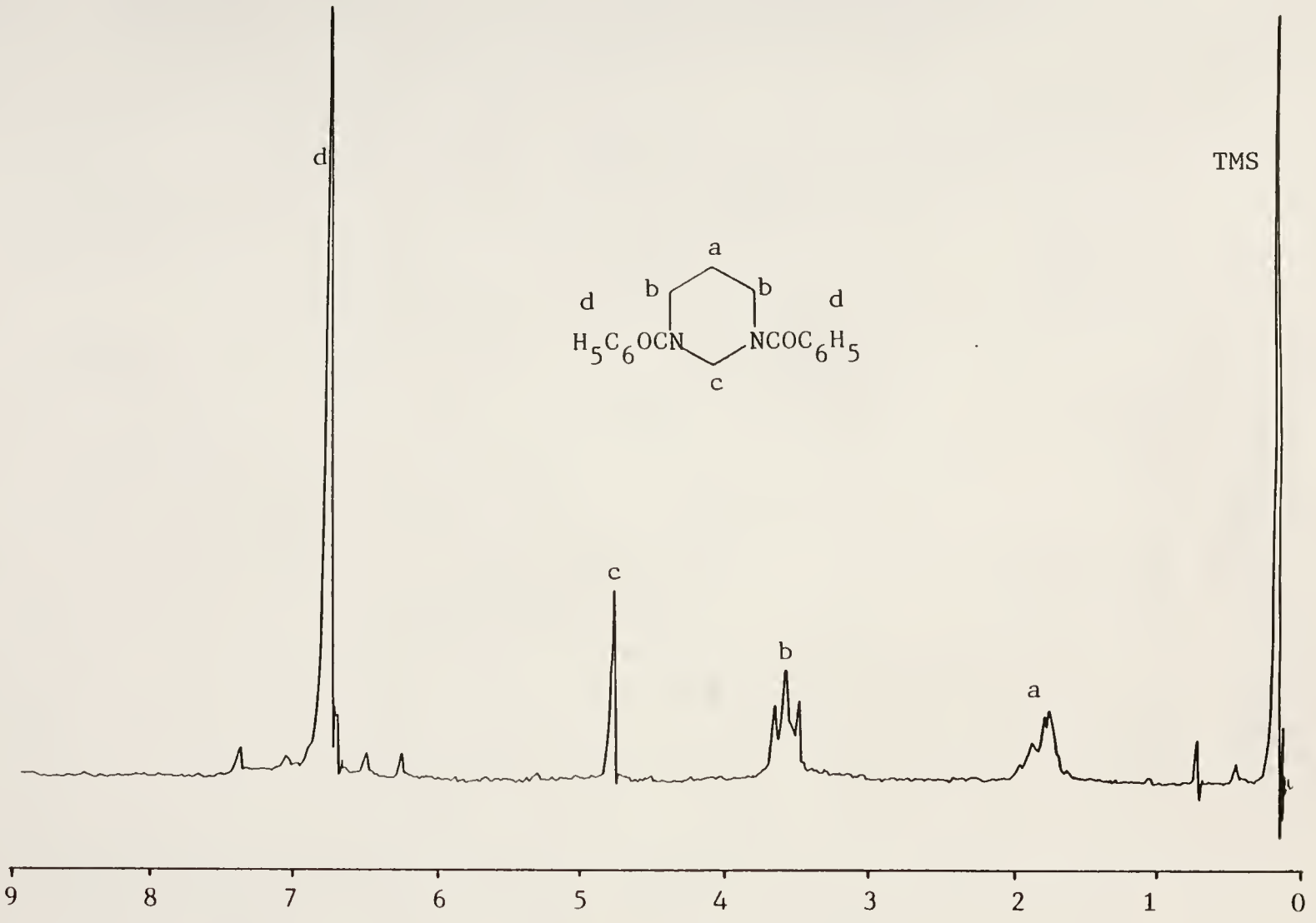


Fig. 3.5 60 MHz ^1H NMR Spectrum of 1,3-Dibenzoylhexahydropyrimidine (in $CDCl_3$) at 25°C.

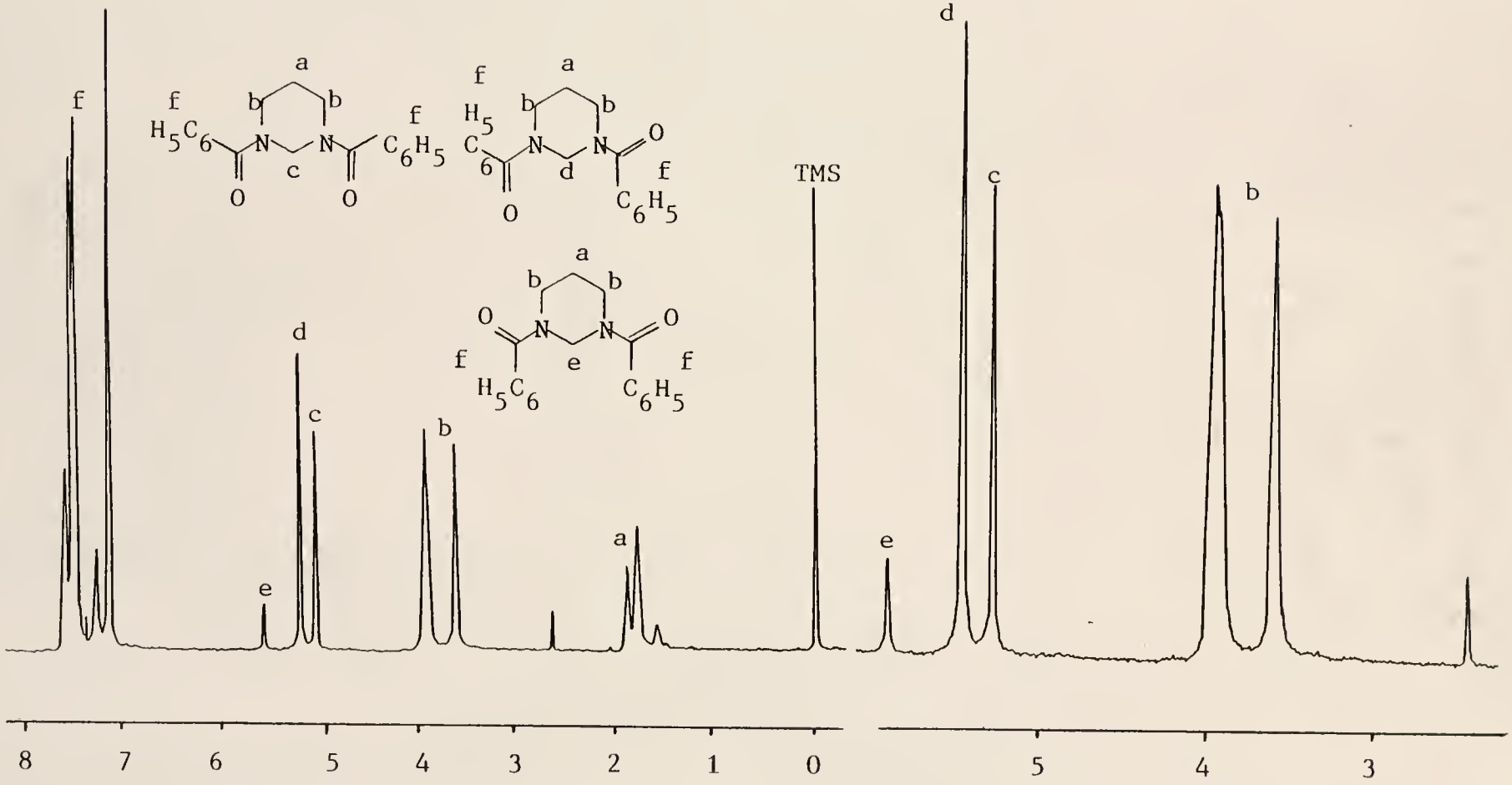


Fig. 3.3 300 MHz ^{1}H NMR Spectrum of 1,3-Dibenzoylhexahydropyrimidine (in $CDCl_3$) at - 30°C.

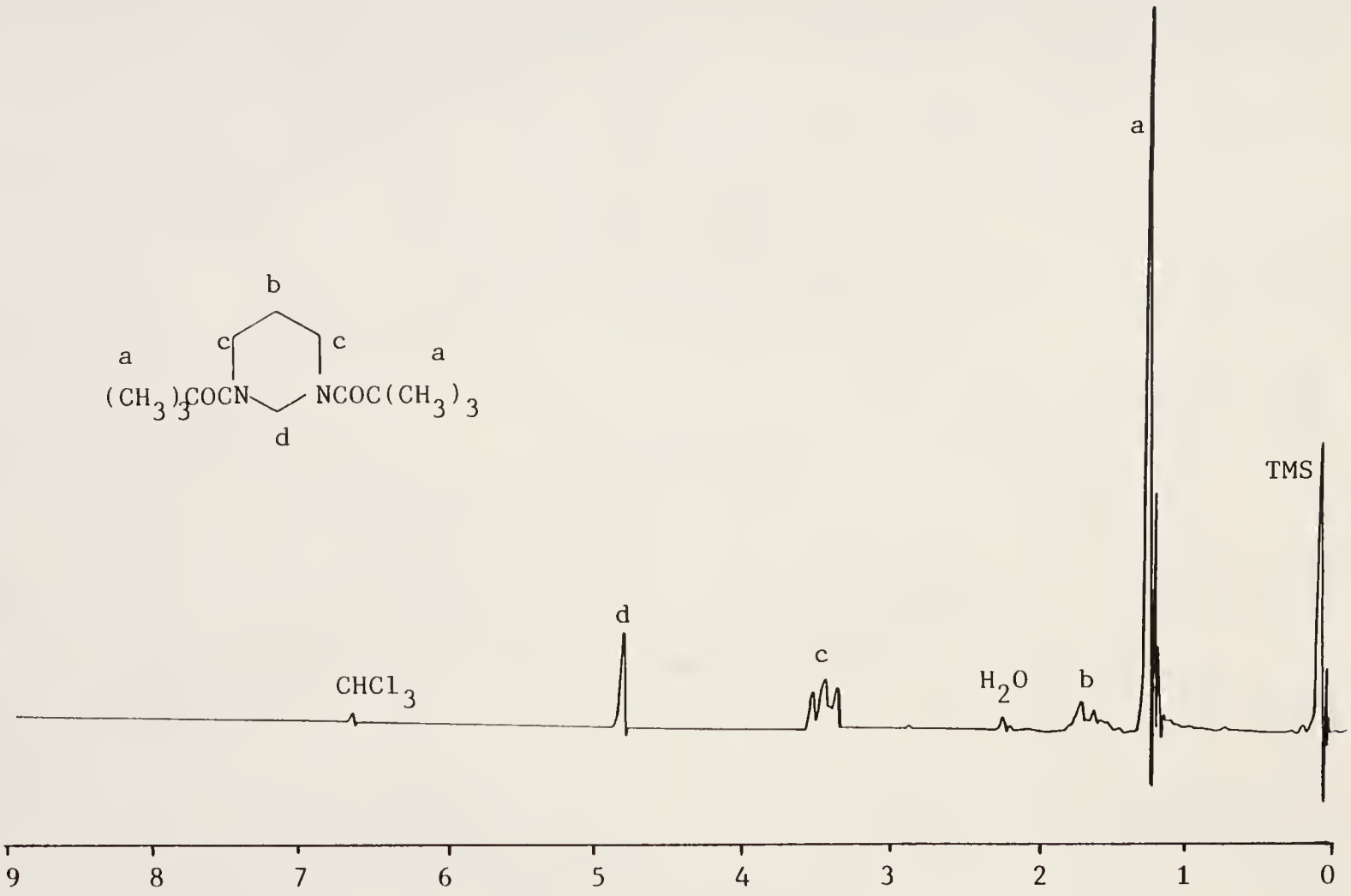


Fig. 3.7 60 MHz ^{1}H NMR Spectrum of 1,3-Dipivaloylhexahydropyrimidine (in $CDCl_3$) at 25°C.

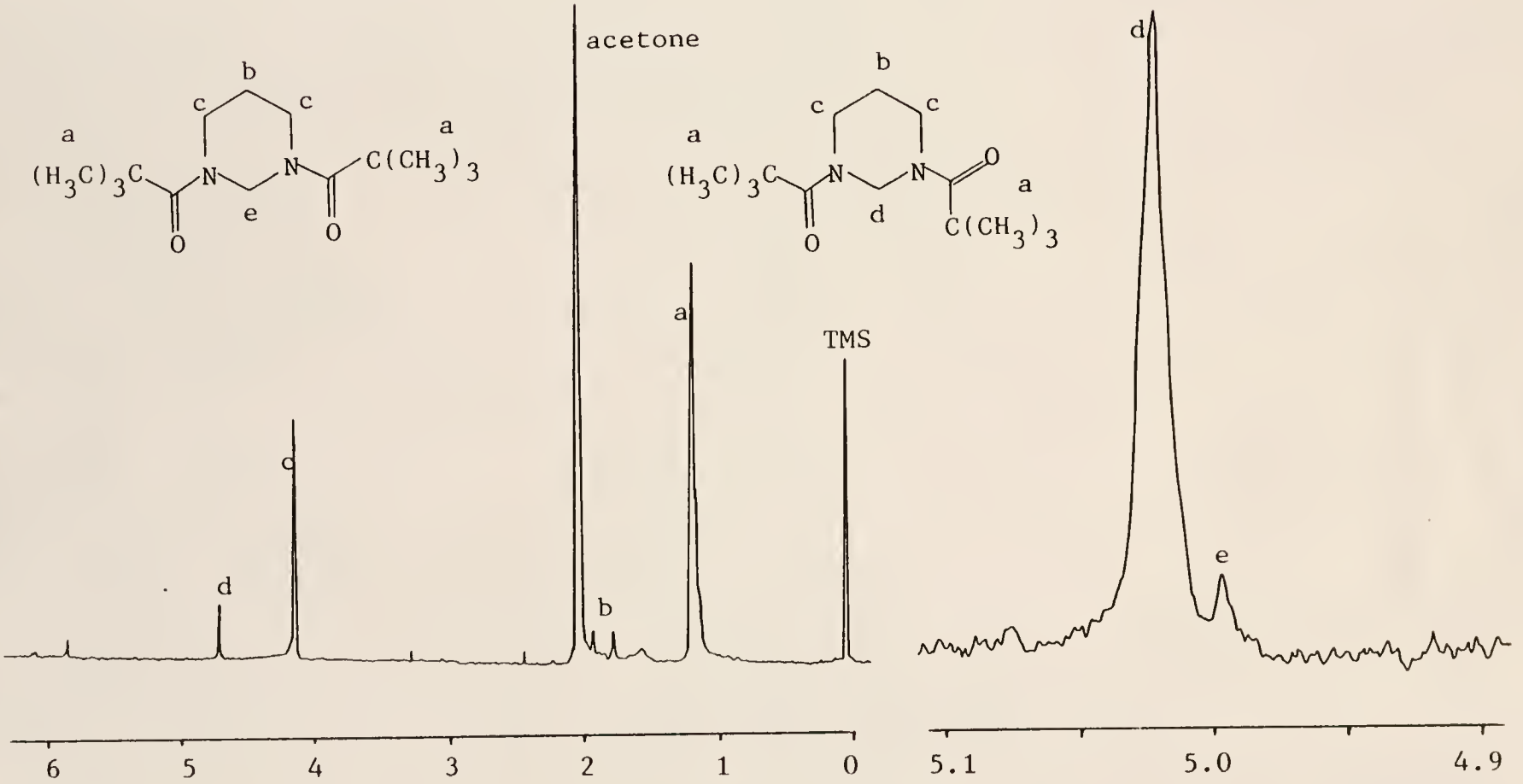


Fig. 3.3 300 MHz ^1H NMR Spectrum of 1,3-Dipivaloylhexahydropyrimidine (in CD_3COCD_3) at -103°C.

Table 3.2 ^{1}H NMR Chemical Shifts (ppm) and Relative Population (%) for 1,3-Diacylhexahydropyrimidines (3.5) and (3.6)

Temp.	compound	2-CH_2		popn.	4(6)-CH_2		5-CH_2		R	
°C	(conformer)	δ(M)	I	(%)	δ(M)	I	δ(M)	I	δ(M)	I
25[a]	(3.5)	5.17(s)	2.00[b]	-	3.81(t)[c]	4.00	1.80(m)	2.02	7.40(m)	10.4
-30[d]	(3.5a)	5.04(s)	0.79	39.7	3.95(m)	4.30[e]	1.84[f](m)	2.01[e]	7.34(m)	10.5[e]
	(3.5b)	5.20(s)	1.06	53.3	3.95(m)	-	1.93[f](m)	-	7.34(m)	-
					3.66(m)					
	(3.5c)	5.57(s)	0.14	7.0	3.66(m)	-	1.84[f](m)	-	7.34(m)	-
25[a]	(3.6)	5.31(s)	2.00[b]	-	3.76(t)[c]	4.00	1.70(m)	2.03	1.28(s)	18.00
-10[d]	(3.6a)	4.99(s)	0.16	8.0	4.41(m)	4.40[e]	1.78(m)	2.04[e]	1.16(s)	19.0[e]
	(3.6b)[g]	5.03(s)	1.84	92.0	4.41(m)	-	1.78(m)	-	1.16(s)	-

M = multiplicity; t = triplet; s = singlet; I = intensity. [a] 60 MHz spectrum. [b] Intensity reference standard; at low temperature total intensity for these peaks taken as 2.0. [c] Being at low field (60 MHz) this signal is seen as an apparent triplet with J = 6 Hz. [d] 300 MHz spectrum. [e] Individual intensities not measurable due to overlap. [f] Tentative assignment. [g] No peaks for (3.6c) observed.

The equilibrium at -30°C for (3.5) favored conformer (b) over (a) by 0.14 kcal $mole^{-1}$ and conformer (b) over (c) by 0.98 kcal $mole^{-1}$. However, for (3.6), the equilibrium at -103°C favored conformer (b) over (a) by 0.83 kcal $mole^{-1}$.

3.2.5. 1,3,5-Triacylhexahydro-sym-triazines Conformational Equilibria from ^1H NMR Spectra

At 25°C compounds (3.7) (figure 3.9) and (3.8) (figure 3.11) showed a 6H singlet for the three CH_2 protons, demonstrating rapid rotation about all three amide links. As the temperature was lowered the peaks broadened and split, and at -30°C separate signals were observed for (3.7) (figure 3.10) for each of the two conformers. However, for (3.8) only one conformer (x) was observed even for spectra recorded as low as -110°C using acetone-d_6 as the solvent (Table 3.3) (scheme 3.4).

Signal assignments shown in Table 3.3 follow the same rules observed for signal assignment for imidazolidines (3.3) and (3.4), i.e., the protons syn to the carbonyl oxygen were shielded. The methylene protons for (3.7) at -30°C showed four singlets, of which three signals were of

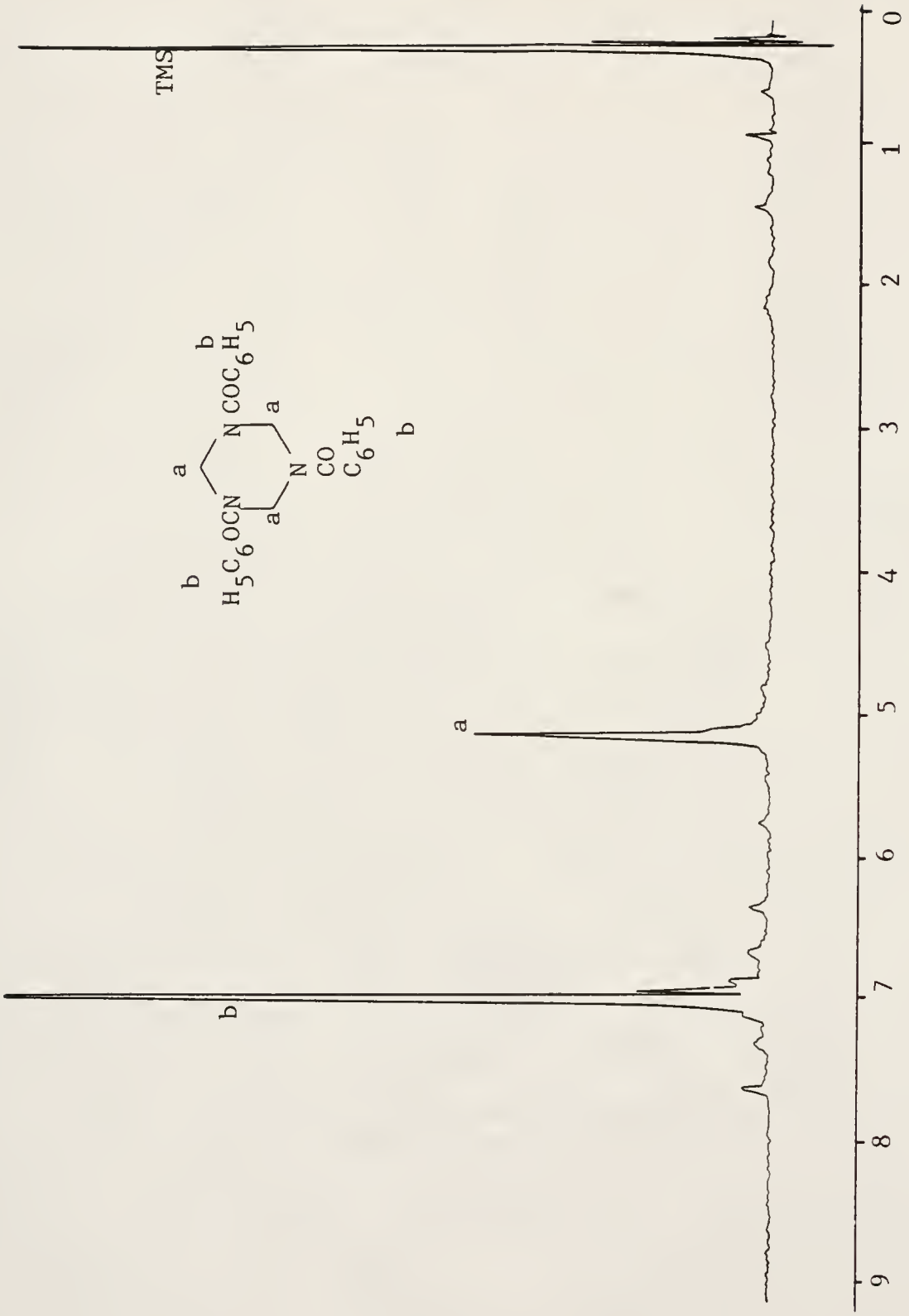


Fig. 3.9 60 MHz ^1H NMR Spectrum of 1,3,5-Tribenzoylhexahydro-sym-triazine (in $CDCl_3$) at 25°C.

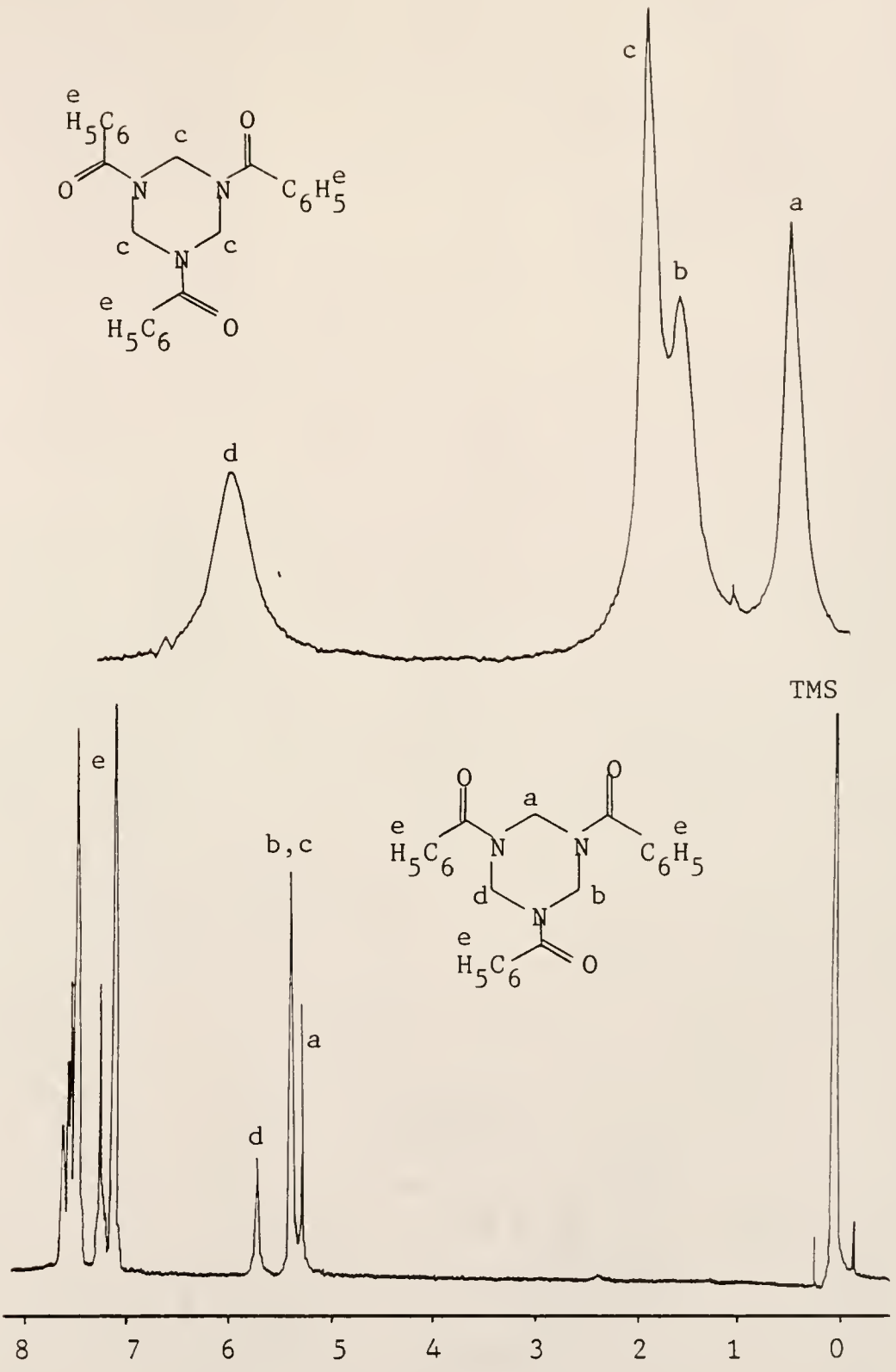


Fig. 3.10 300 MHz ^{1}H NMR Spectrum of 1,3,5-Tribenzoyl-hexahydro-sym-triazine (in $CDCl_3$) at -30°C.

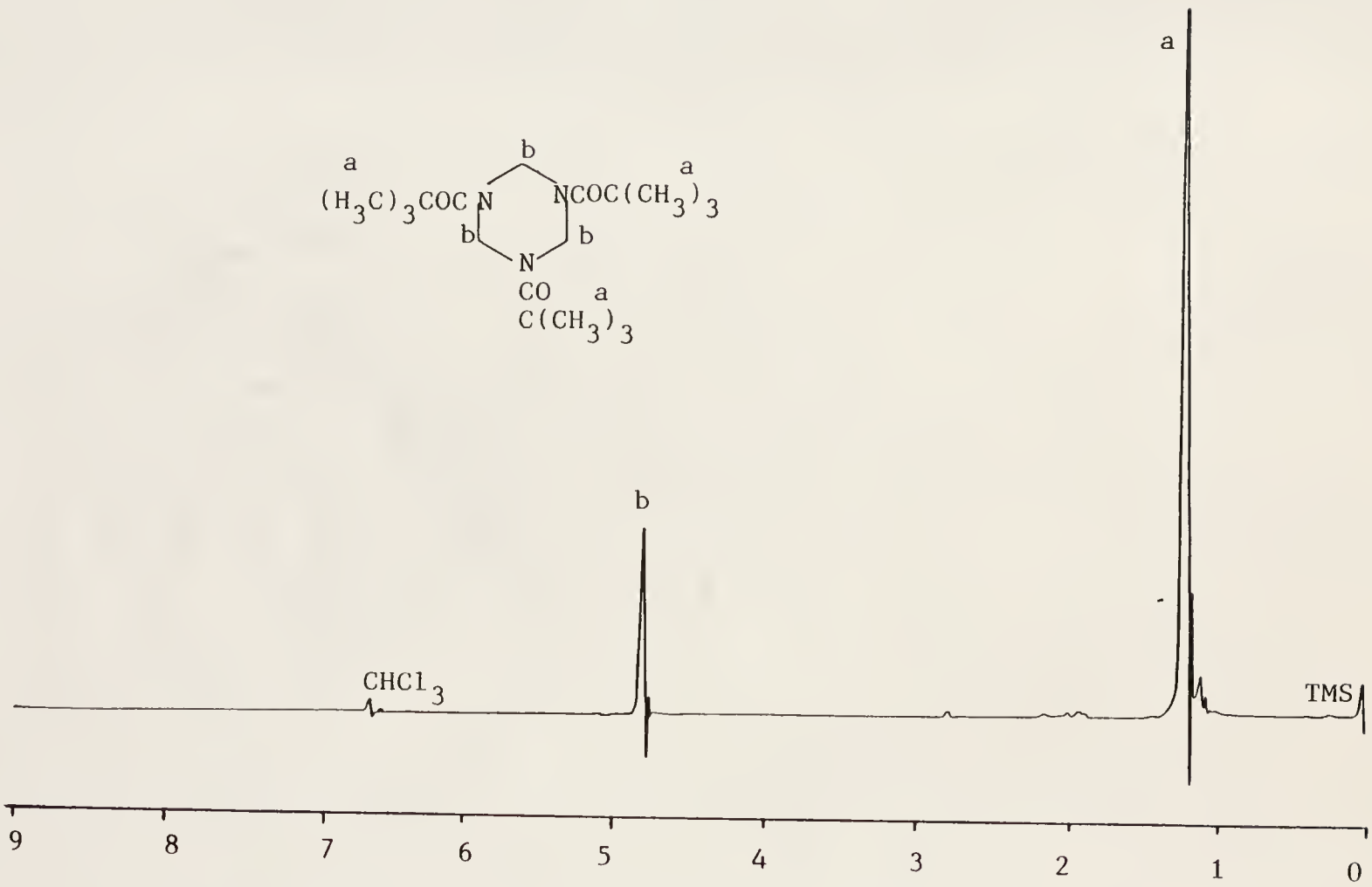


Fig. ..11 60 MHz ^1H NMR Spectrum of 1,3,5-Tripivaloylhexahydro-sym-triazine (in $CDCl_3$) at 25°C.

Table 3.3 ^{1}H NMR Chemical Shifts (ppm) and Relative Population (%) for 1,3,5-Triacylhexahydro-sym-triazines (3.7) and (3.8)

Temp.	compound	2,4,6-CH_2		popn.	N-substit.	
°C	(conformer)	δ(M)	I	(%)	δ(M)	I
25[a]	(3.7)	5.30(s)	6.00[b]	-	7.40(s)	15.2
-30[c]	(3.7x)	5.38(s)	2.19	36.5	7.40(m)	[d]
	(3.7y)	5.26(s)	3.81[e]	63.5	7.40(m)	[d]
		5.37(s)				
		5.71(s)				
25[a]	(3.8)	5.40(s)	6.00[b]	-	1.35(s)	27.4
-100[c]	(3.8x)[f]	5.39(s)	6.00	100.0	1.33(s)	27.3

M = multiplicity; s = singlet; m = multiplet; I = intensity. [a] 60 MHz spectrum. [b] standard reference intensity. [c] 300 MHz spectrum. [d] Total intensity 15.1; individual intensities not measurable due to overlap. [e] Total intensities of the three signals together. [f] Signals for (3.8y) not observed, even at -110°C.

equal intensity corresponding to conformer (3.7y). The one remaining signal was assigned to conformer (3.7x), in which all methylene protons are identical.

Relative signal intensities and the isomer proportions from the 2,4,6-CH_2 signals are shown in Table 3.3. For (3.7) (x):(y) = 36.5:63.5% and for (3.8) (x):(y) = 100:0%.

For the equilibrium at -30°C (3.7) favored conformer (y) over (x) by 0.26 kcal $mole^{-1}$. However, (3.8) was found to exist exclusively in the (x) conformer.

3.2.6. 1,3-Diacylimidazolidines Conformational Study from ^{13}C NMR Spectra

The 75 MHz spectra of (3.3) (figure 3.12) at 25°C were near coalescence, and showed broadened lines for C-2, C-4 and C-5 which became sharp singlets at 60°C; (3.4) (figure 3.14) showed sharp singlets for these carbons at 25°C. At -30°C for (3.3) (figure 3.13) and -70°C for (3.4) (figure 3.15), signals were seen for the individual conformers (Table 3.4). The signals were assigned to different conformers based on the model compounds discussed earlier (see section 3.2.2).

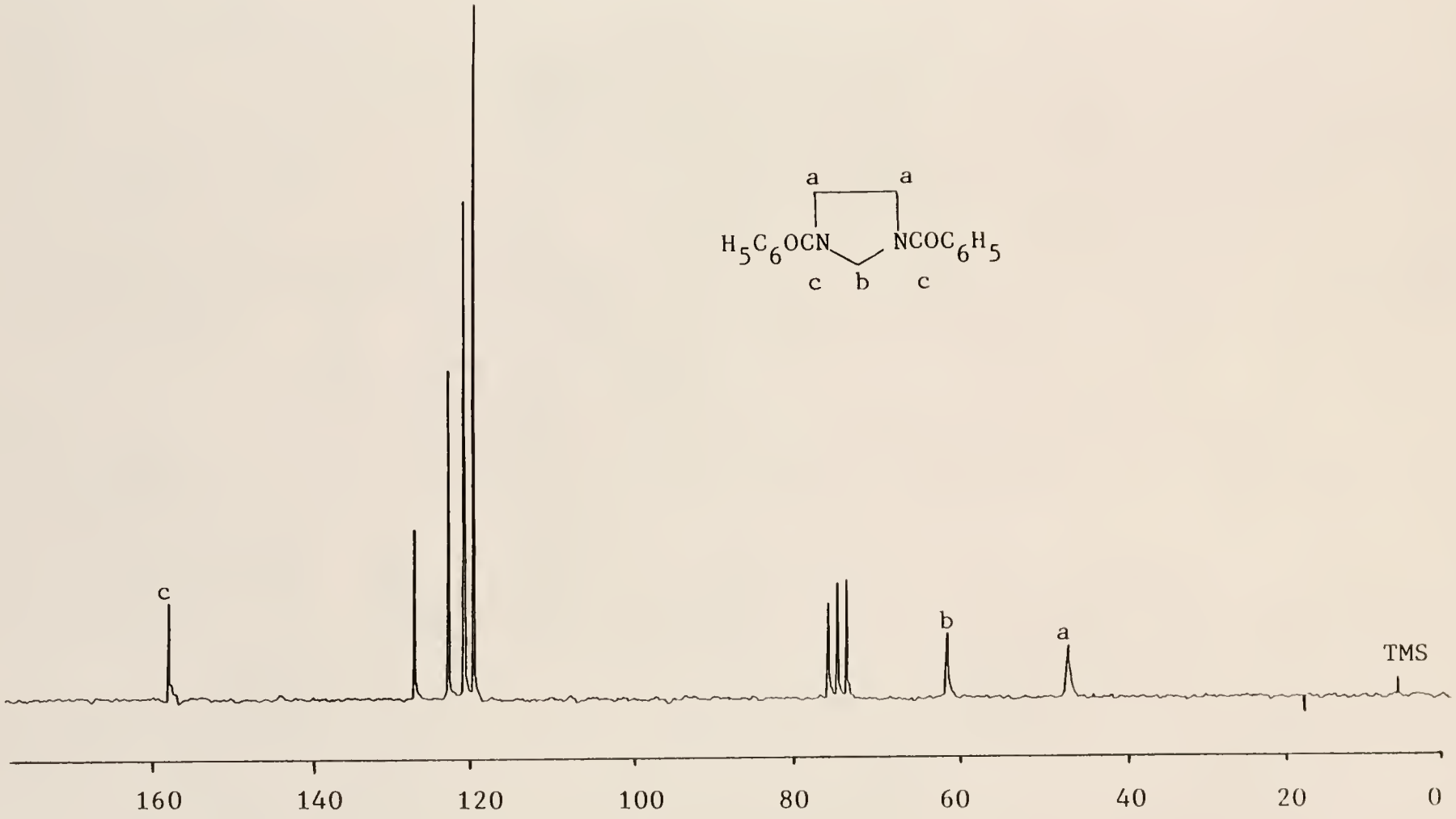


Fig. 3.12 25 MHz ^{13}C NMR Spectrum of 1,3-Dibenzoylimidazolidine (in $CDCl_3$) at 60°C.

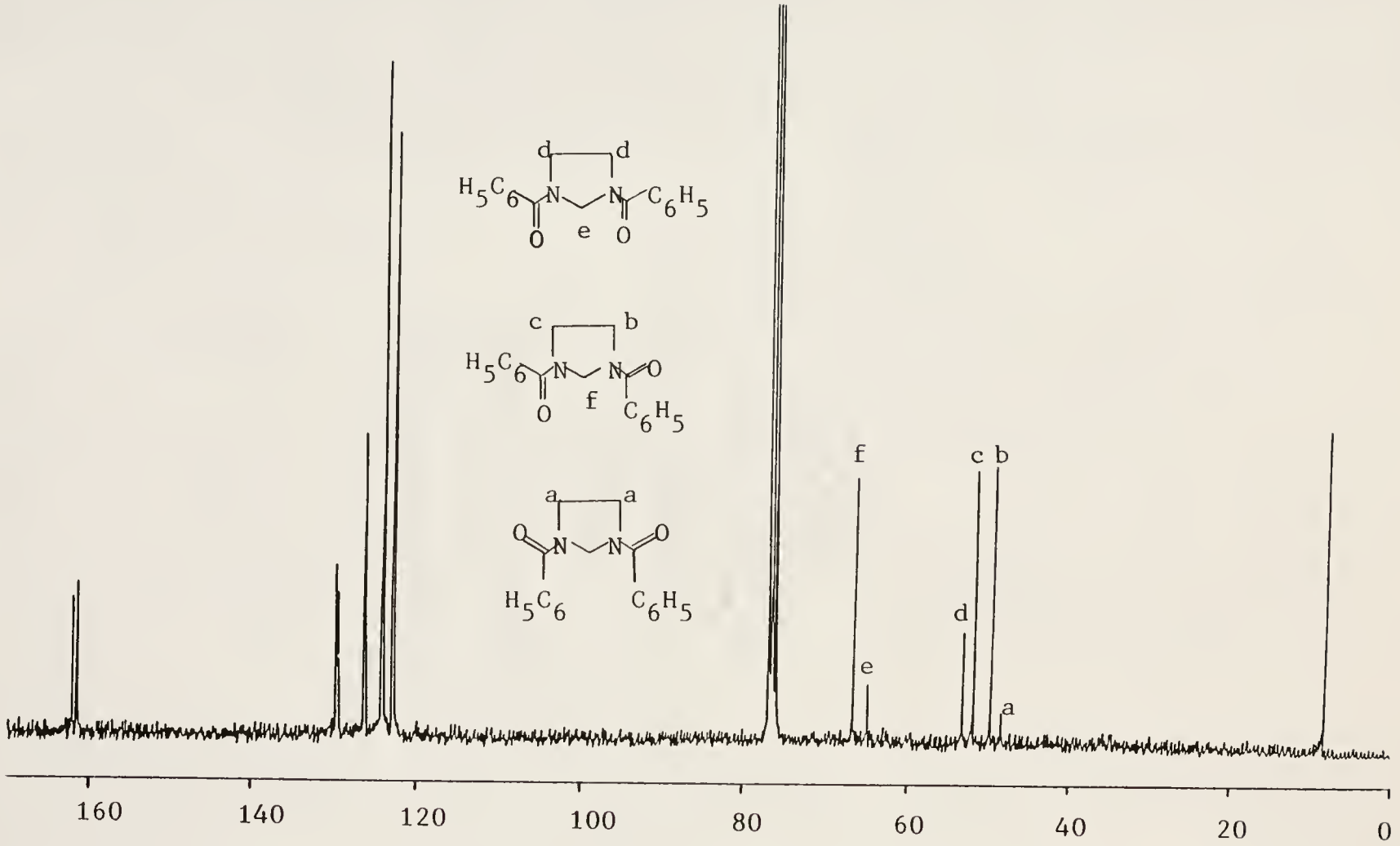


Fig. ..13 75 MHz ^{13}C NMR Spectrum of 1,3-Dibenzoylimidazolidine (in $CDCl_3$) at -30°C.

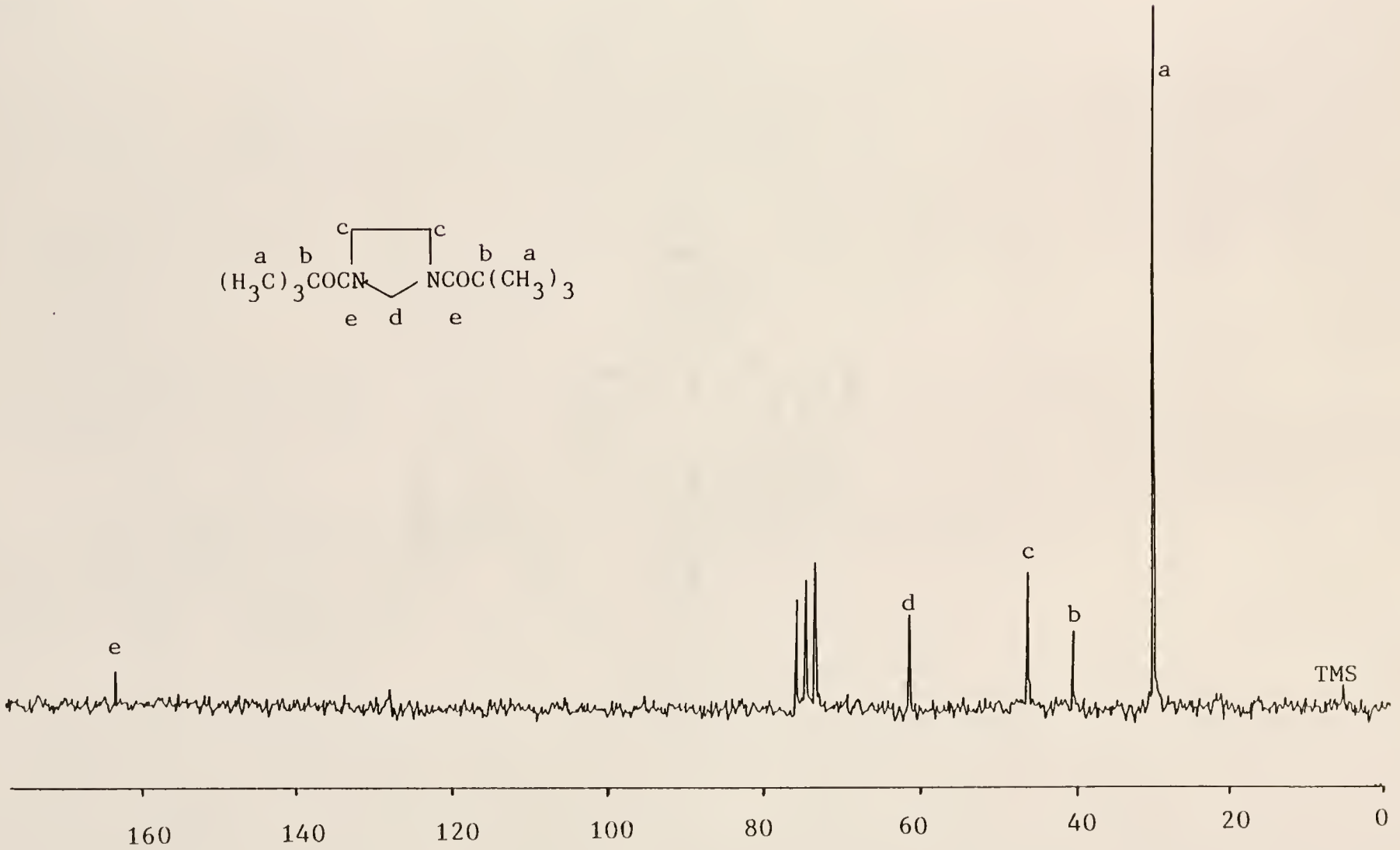


Fig. 3.14 25 MHz ^{13}C NMR Spectrum of 1,3-Dipivaloylimidazolidine (in $CDCl_3$) at 25°C.

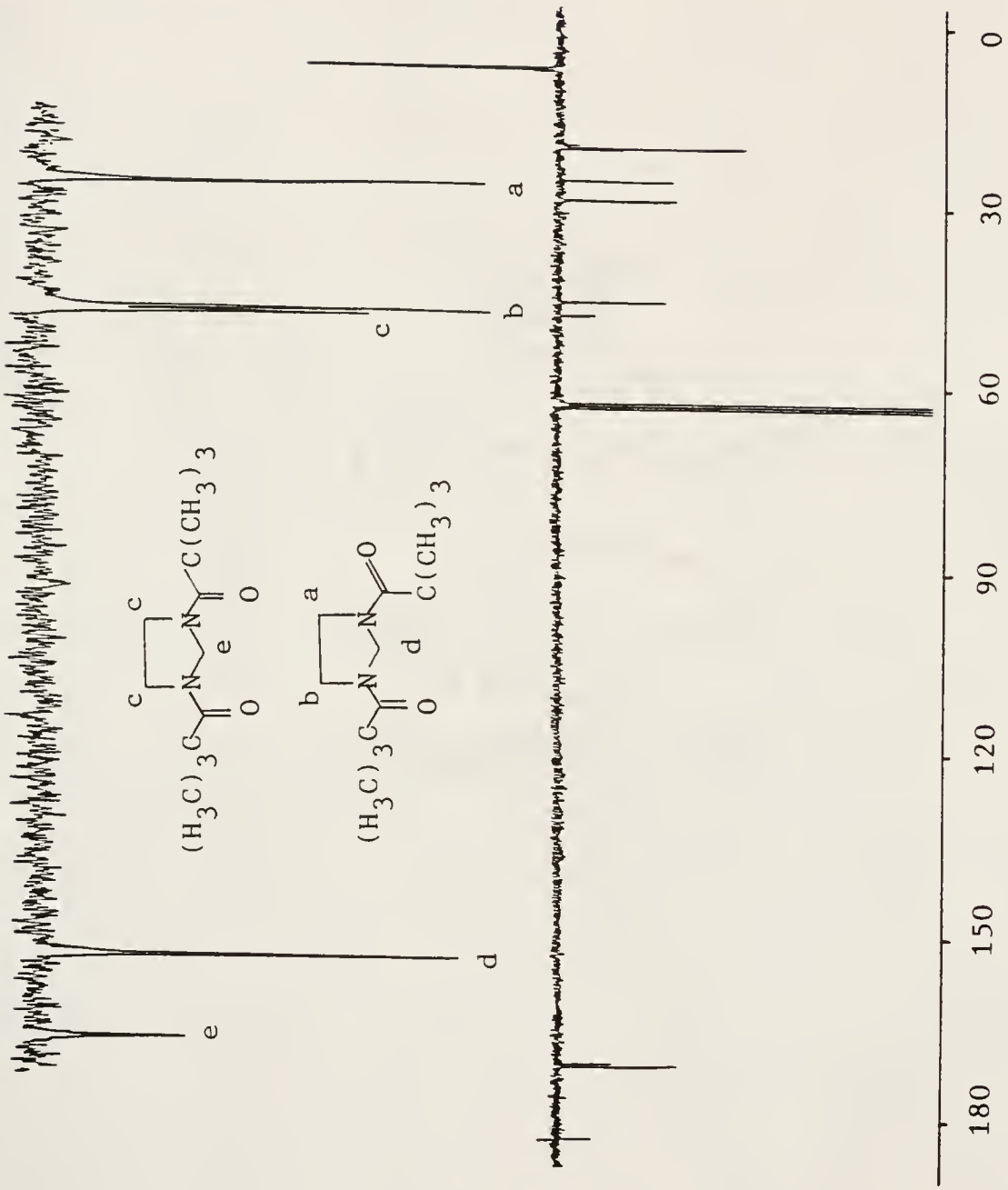


Fig. 3.15 75 MHz ^{13}C NMR Spectrum of 1,3-Dipivaloylimidazolidine (in $CDCl_3$) at −70°C.

Table 3.4 ^{13}C NMR Shifts (δ, ppm) for 1,3-Diacylimidazolidines (3.3) and (3.4).

Comp. no.	Temp. °C	Confor-mation	Imidazolidine ring			R-substituent C_6H_5 or $C(CH_3)_3$				C=O
			C_2	C_4	C_5	C_1	C_2,C_6[a]	C_3,C_5[a]	C_4	
(3.3)	50[b]		62.0	45.7	45.7	135.1	127.1	128.4	130.6	168.8
	25[b]		[c]	[c]	[c]	134.8	127.0	128.3	130.5	168.7
	-30[d]	(3.3a)	60.4	48.0	48.0	134.4[a]	126.9	127.3	130.8[a]	[e]
		(3.3b)	62.3	44.2	46.5	134.6[a]	127.0	128.5	130.9[a]	169.4
										168.8
		(3.3c)	[e]	42.8	42.8	134.7[a]	127.2	128.7	131.1[a]	168.6
(3.4	25[b]		62.3	45.5	45.5	38.8	27.2			175.8
	-70[d]	(3.4a)	61.7	46.6	46.6	38.7[a]	26.80[a]			175.3
		(3.4b)	63.7	46.5	43.6	38.6[a]	26.74[a]			175.8
										175.7
		(3.4c)	[e]	[e]	[e]	38.5[a]	26.70[a]			[e]

[a] Tentative assignment. [b] 25 MHz spectrum. [c] one broad unresolved peak. [d] 75 MHz spectrum.
[e] Not observed.

For compound (3.3) conformers (3.3a), (3.3b) and (3.3c) showed a total of four signals due to C-4 and C-5 carbons. Of these, the two intermediate chemical shifts were of equal intensity and were unambiguously assigned to the conformer (3.3b). From the rule stated above, that the carbon syn to the carbonyl oxygen was shielded, the medium intensity peak at 48.0 ppm was assigned to (3.3a) and the low intensity peak at 42.8 ppm to (3.3c). (These assignments are in fair agreement with the conformer populations deduced from the proton spectra). For the C-2, only two signals were obtained; the peak of higher intensity was assigned to (3.3b) and the other one being at a higher field than that for (3.3b) was assigned to (3.3a). The expected peak for the least populated isomer (3.3c) was not observed.

Compound (3.4) displayed only three peaks for the 4,5-carbon atoms: two of equal and high intensity were unambiguously assigned to (3.4b); the less intense peak at lower field was assigned to (3.4a), again based on the rule that the carbon syn to the carbonyl oxygen was shielded. With conformer (3.4c) being the least populated, (cf proton spectra) its peaks were not observed. Similarly, for the C-2 carbon, peaks were found only for (3.4a) and (3.4b).

The ^{13}C chemical shift assignments of the phenyl group in (3.3) and the t-butyl group in (3.4) were based on the difference in intensity of the signals, the off-resonance spectra, and for R=C_6H_5 comparison with the spectrum of (3.12). In compound (3.3), the C-2,6 and C-3,5 carbons of the phenyl ring showed relatively intense signals (doublets in off-resonance spectrum), and C-1 a low intensity signal (singlet in off-resonance spectrum). In compound (3.4), the quaternary carbon of $C(CH_3)_3$ showed a low intensity signal at ca. 38 ppm, and the methyl groups gave a very intense signal at higher field. The lowest field signal in the spectra of compounds (3.3) and (3.4) was that of the carbonyl carbons. The low temperature spectrum, of each of the compound showed three C=O signals of which the two of equal intensity were assigned to the two carbonyl groups in conformer (b). The signal due to the least populated conformer, (a) in (3.3) and (c) in (3.4), was not observed.

3.2.7 ^{13}C 1,3-Diacylhexahydropyrimidines Conformational Study from ^{13}C NMR Spectra

The 75 MHz spectrum of (3.5) (figure 3.16) at 25°C was near coalescence and showed broadened signals for C-2, C-4, C-5 and C-6 which became sharp signals at 60°C; (3.6) (figure 3.18) shows sharp signals for the ring carbons at

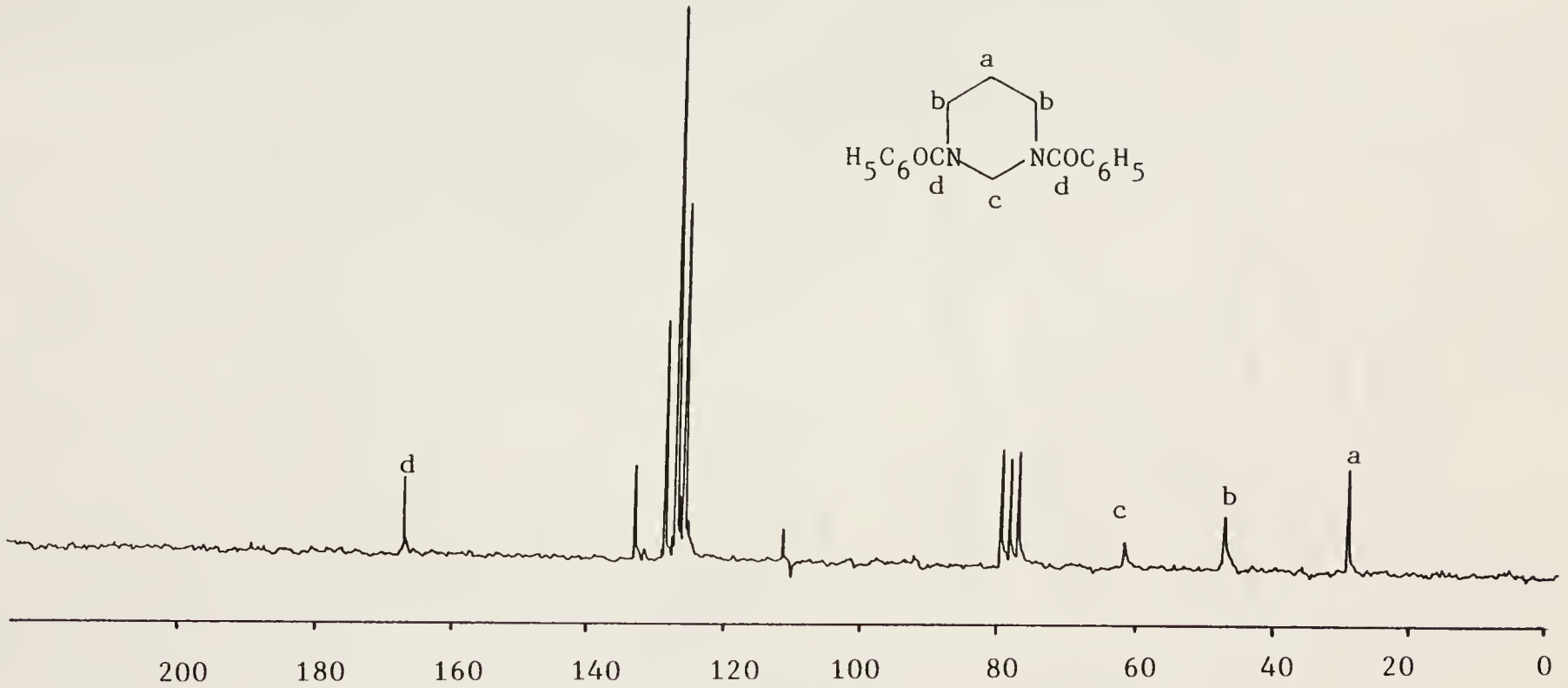


Fig. 3.16 25 MHz ^{13}C NMR Spectrum of 1,3-Dibenzoylhexahydropyrimidine (in $CDCl_3$) at 60°C.

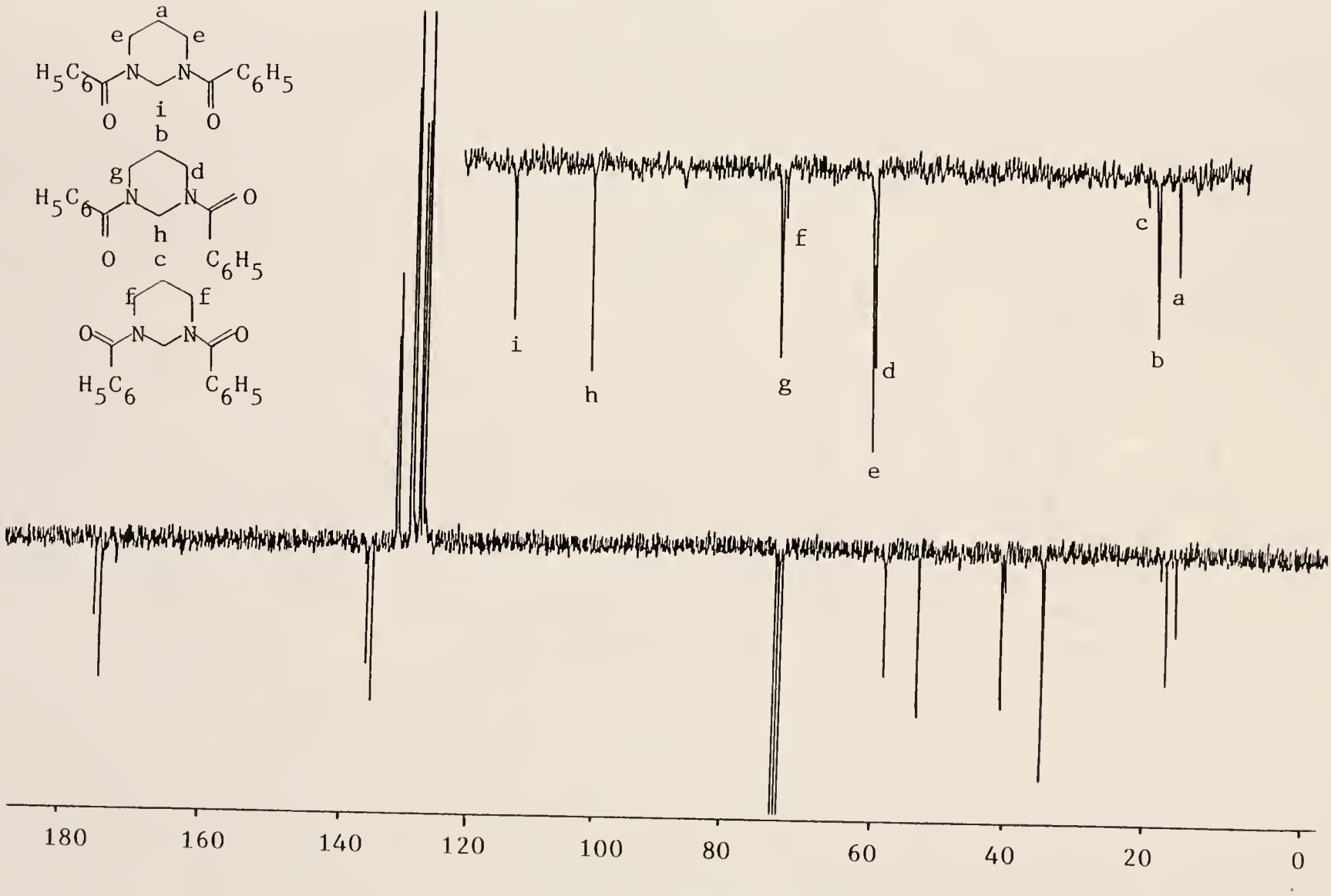


Fig. 3.17 75 MHz ^{13}C NMR Spectrum of 1,3-Dibenzoylhexahydropyrimidine (in $CDCl_3$) at -40°C.

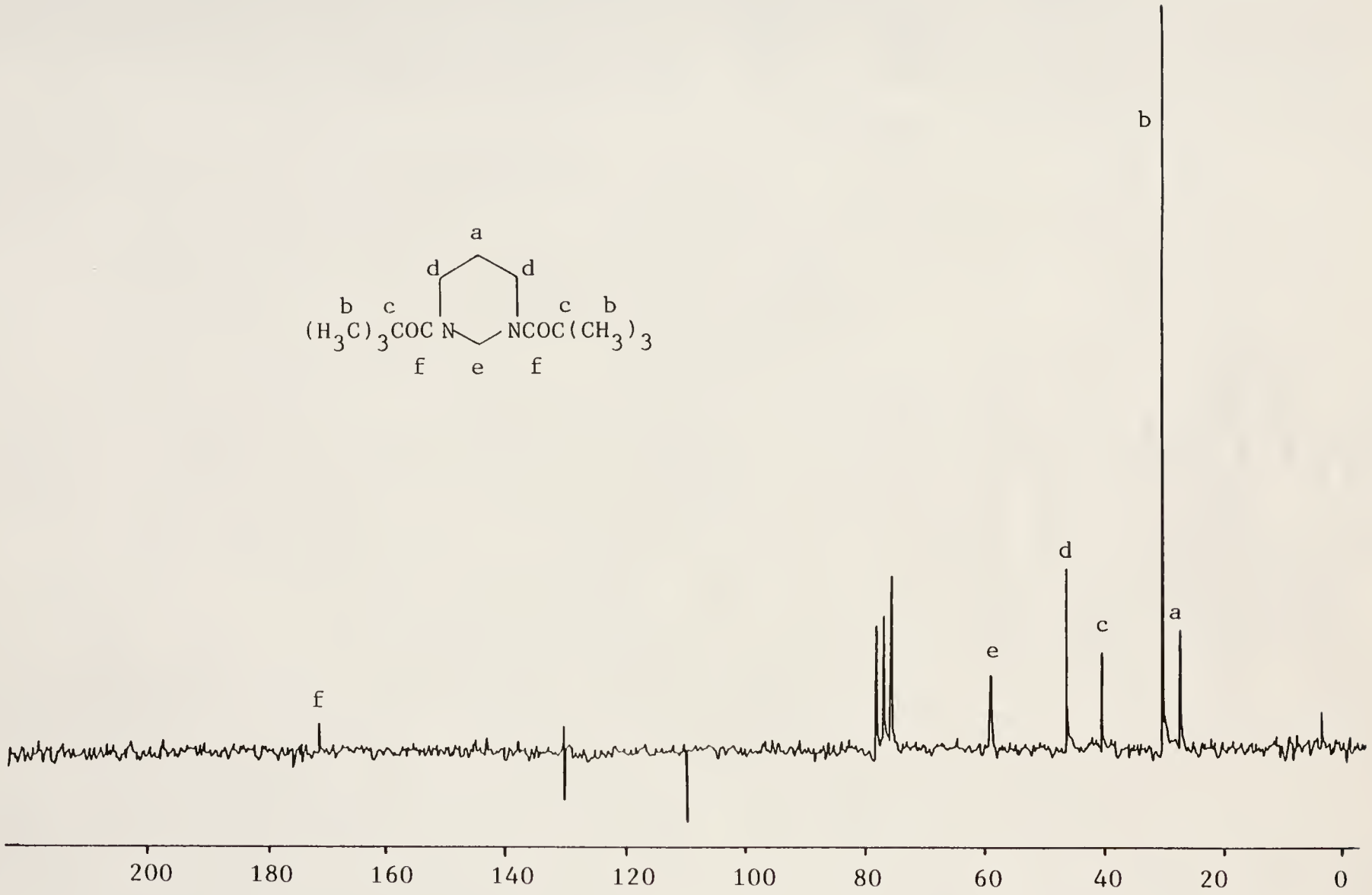


Fig. 3.18 25 MHz ^{13}C NMR Spectrum of 1,3-Dipivaloylhexahydropyrimidine (in $CDCl_3$) at 25°C.

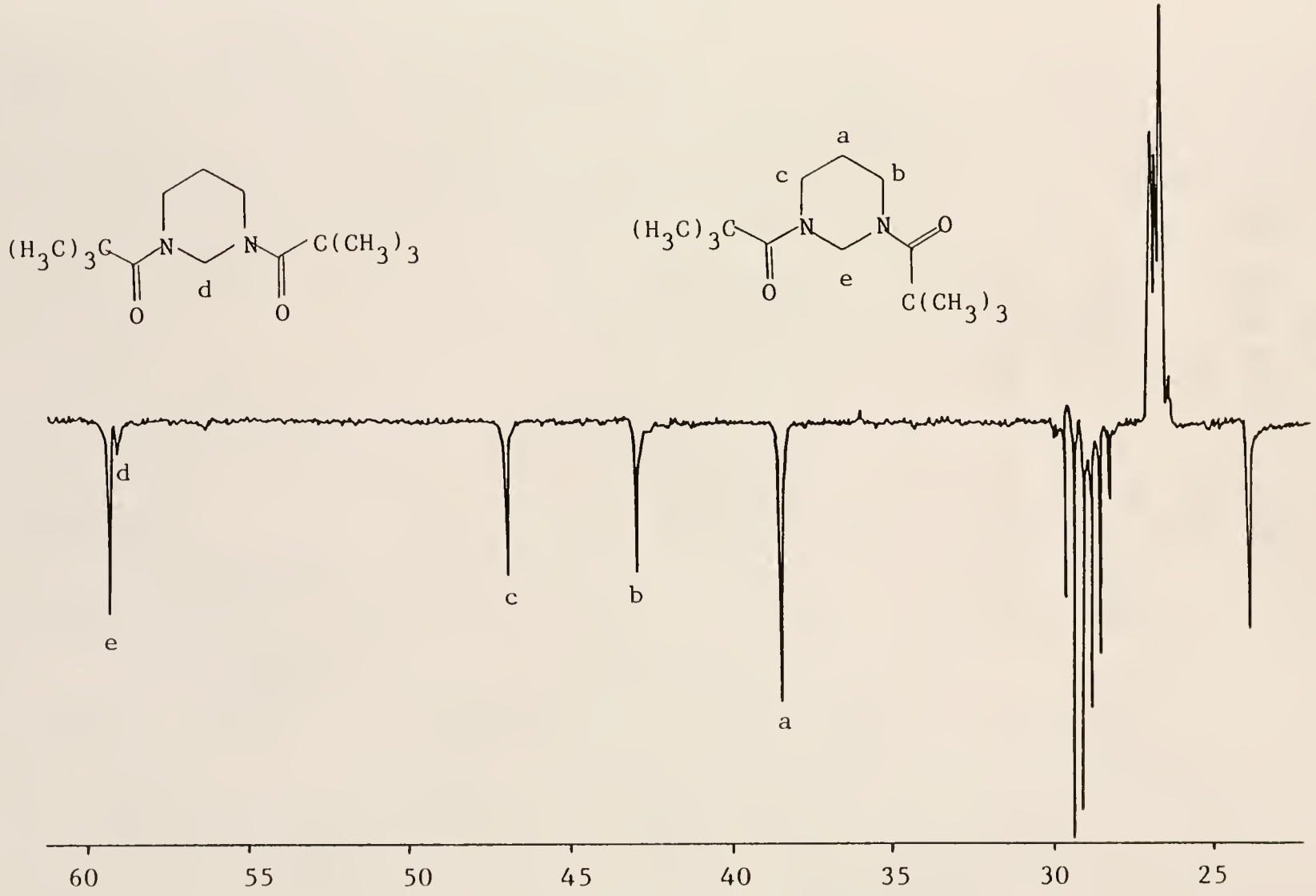


Fig. 3.19 75 MHz ^{13}C NMR Spectrum of 1,3-Dipivaloylhexahydropyrimidine (in CD_3COCD_3) at -100°C.

25°C. At -40°C signals for the individual conformers appeared in the spectrum of (3.5) (figure 3.17). However, for (3.6) at -70°C separate signals were seen only for two conformers as was described above for the ^{1}H spectrum (figure 3.19).

Signals were assigned by reference to model compounds as discussed earlier. The C-5 carbon gave an additional signal around 24.5 ppm. The assignments of Table 3.5 follow these considerations. An illustration for the C-2 carbons of (3.5) and (3.6) is as follows; at -40°C (3.5) showed three signals for the C-2 carbon. Using the rule that the carbon syn to the carbonyl was the most shielded, the most downfield signal was assigned to (3.5c), the most upfield signal to (3.5a) and the remaining one to (3.5b). Based on similar considerations, of the two signals seen for the C-2 carbon of (3.6), the most intense was assigned to (3.6b). Since the remaining one was at a higher field than (3.6b), it was assigned to (3.6a). These assignments agree with conformer populations deduced from the proton spectra. Assignments for the C-4-C-6 carbons were made similarly.

Table 3.5 ^{13}C NMR Shifts (δ, ppm) for 1,3-Diacylhexahydropyrimidines (3.5) and (3.6).

Temp. °C	Comp. (conformation)	Pyrimidine Ring C_2	C_4	C_5	C_6	R-Substituent C_6H_5 or $C(CH_3)_3$ C_1	C_2,C_6	C_3,C_5	C_4	C=O
25[a]	(3.5)	59.8	44.3	24.9	44.3	133.2	127.4	128.4	130.3	170.1
-40[b]	(3.5a)	52.8	47.3	25.2[c]	47.3	134.3[c]	127.2[c]	128.4[c]	130.3[c]	169.9
	(3.5b)	58.2	47.0	25.2[c]	41.8	134.0[c]	127.0[c]	128.3[c]	130.2[c]	170.6
						133.9	126.8			169.8
	(3.5c)	62.8	41.7	24.0[c]	41.7	133.3[c]	126.5[c]	128.1[c]	130.0[c]	d
25[a]	(3.6)	58.3	44.9	24.9	44.9	38.7	28.00			176.8
-70[b]	(3.6a)	58.4	47.1	25.6	47.1	39.1	28.2[c]			176.1
	(3.6b)[d]	58.6	47.1	25.6	43.3	39.1	28.3[c]			176.1
						28.1[c]				175.8

[a] 25 MHz spectrum. [b] 75 MHz spectrum. [c] Tentative assignment. [d] Conformer (3.6c) not observed.

3.2.8. 1,3,5-Triacylhexahydro-sym-triazines Conformational Study from ^{13}C NMR Spectra

The 75 MHz spectra of (3.7) (figure 3.19) and (3.8) (figure 3.21) at 25°C showed signals for the three methylene carbons at 58.5 and 57.3 ppm, respectively. At -70°C for (3.7) (figure 3.20), signals were seen for the individual conformers. However, for (3.8) only one conformer (x) was observed even at a temperature as low as -110°C. This was the same result as seen in its ^{1}H spectrum. The signal assignments for the two conformers (x) and (y) of compound (3.7) and one conformer (x) of compound (3.8) were also based on the model compounds discussed earlier. The signal assignments are shown in Table 3.6.

3.2.9. Kinetic Parameters

The kinetic parameters obtained were the free energy difference between conformers and the free energy of activation for the barrier to rotation around the amide C(O)-N bonds. The free energy differences ($\Delta G°$) were calculated from the population ratios (of their C-2 methylene protons signals) obtained for each of the amides from their ^{1}H NMR spectra and are given in table 3.7. Free energies ($\Delta G°$), which are compensated for the entropy factor (for the topomers of unsymmetrical isomers), are also given in table 3.7.

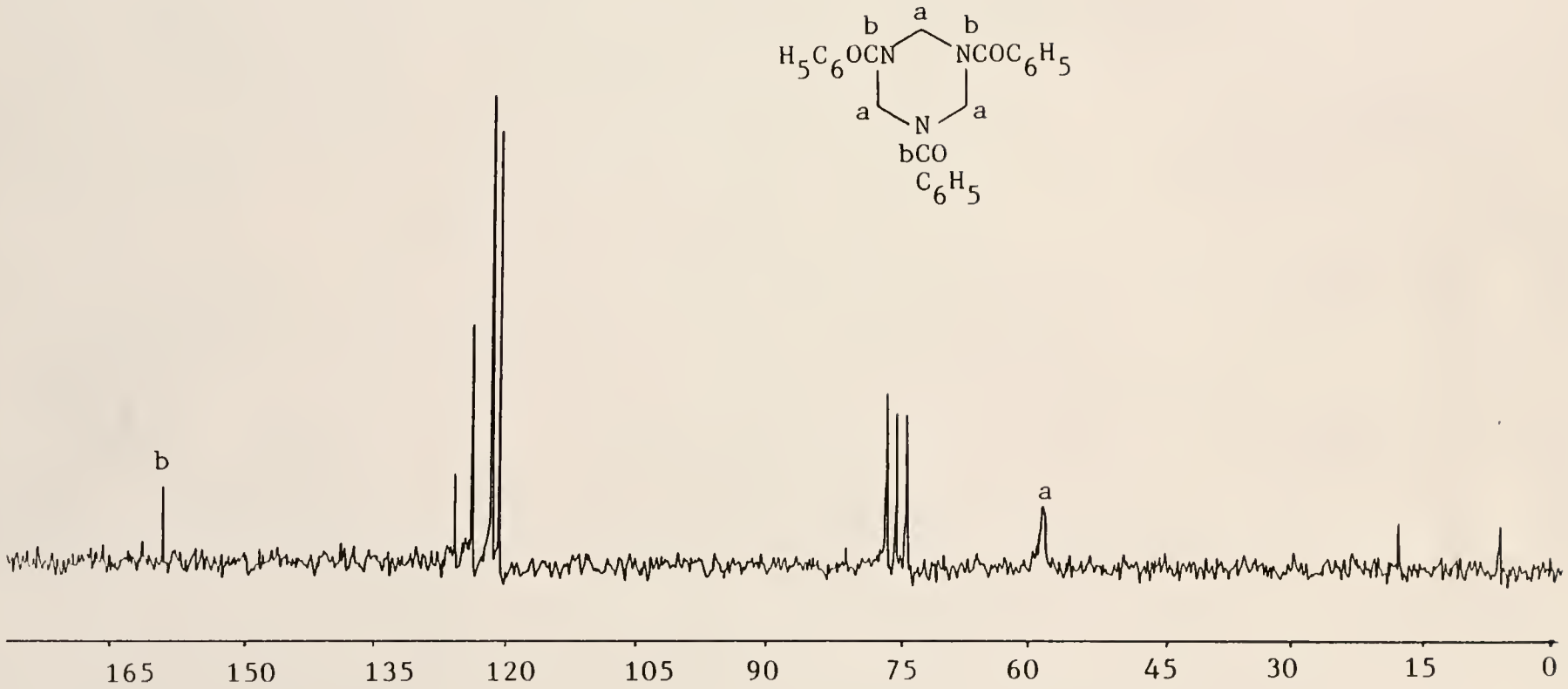


Fig. 3.20 25 MHz ^{13}C NMR Spectrum of 1,3,5-Tribenzoylhexahydro-sym-triazine (in $CDCl_3$) at 25°C.

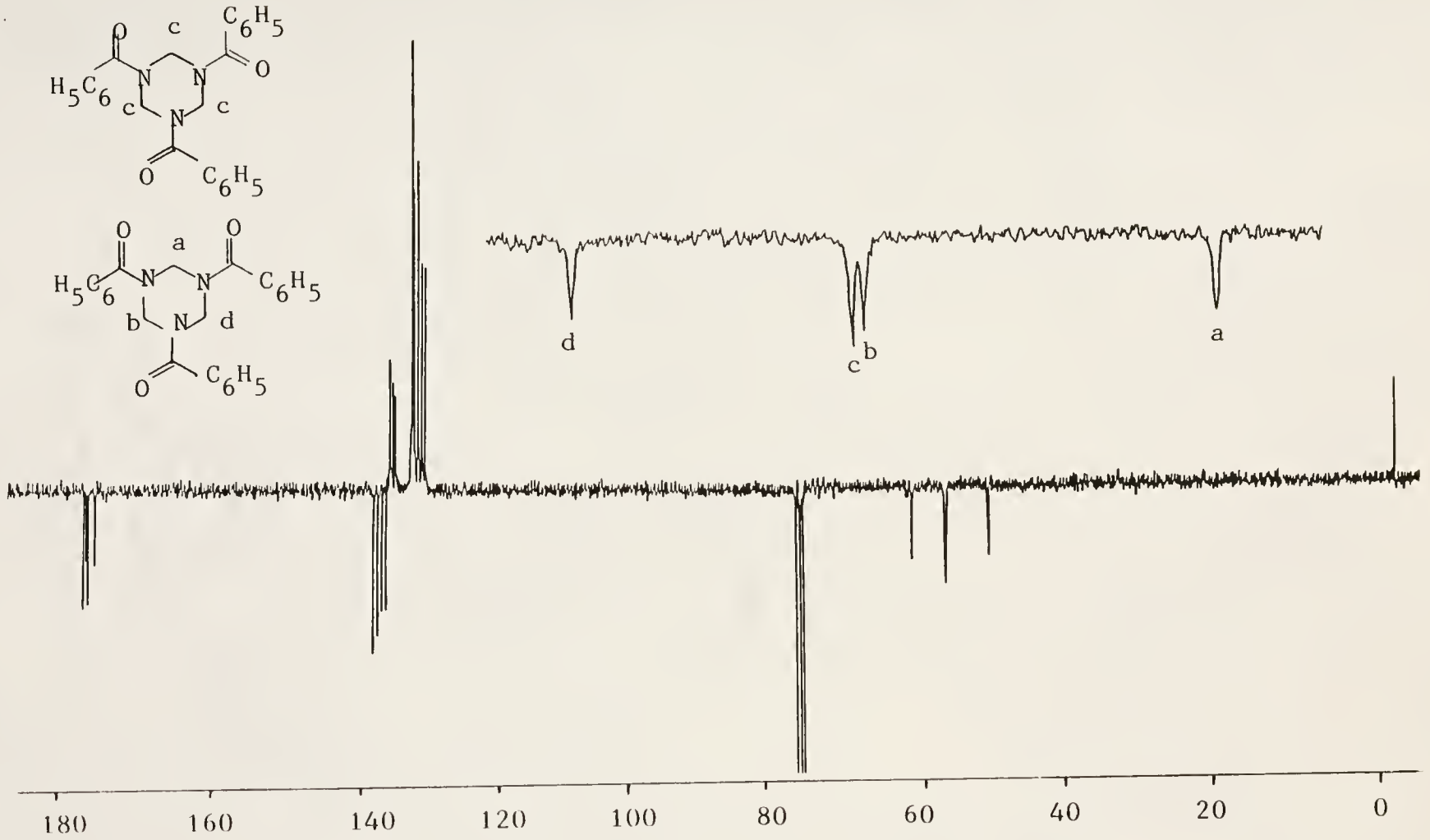


Fig. 2.21 75 MHz ^{13}C NMR Spectrum of 1,3,5-Tribenzoylhexahydro-sym-triazine (in $CDCl_3$) at -30°C.

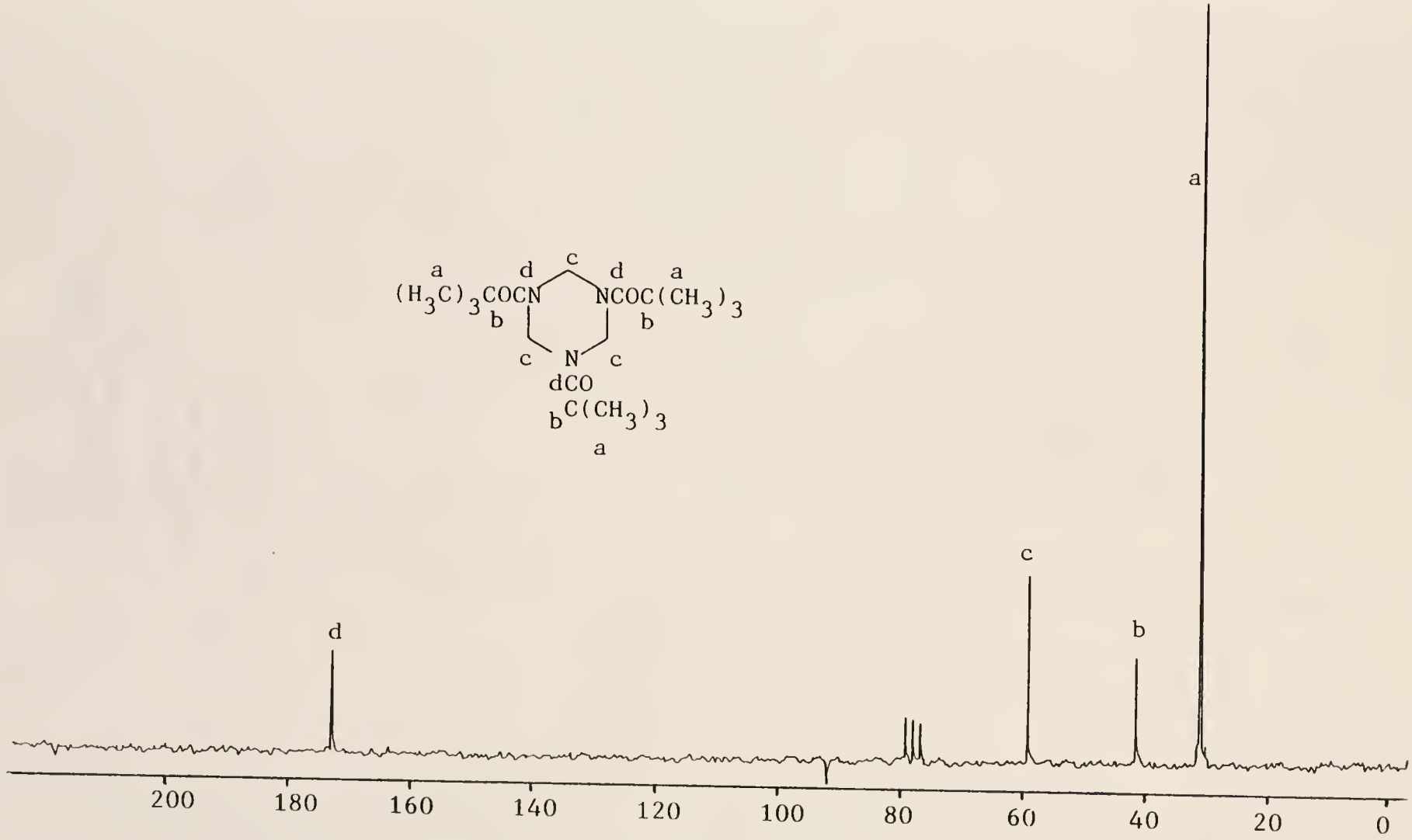


Fig. 3.22 25 MHz ^{13}C NMR Spectrum of 1,3,5-Tripivaloylhexahydro-sym-triazine (in $CDCl_3$) at 25°C.

(3.8).

Temp. °C	Comp. (conformation)	Triazine ring C_2, C_4, C_6	R- substituent C_6H_5 or $C(CH_3)_3$ C_1	$C_2 \cdot C_6$	C_3, C_5	C_4	C=O
25[a]	(3.7)	58.5	133.2	127.5	128.5	131.0	170.5
-70[b]	(3.7x)	58.4	133.5[c]	127.9[c]	128.7[c]	131.4[c]	170.4
	(3.7y)	52.9	132.9[c]	127.8[c]	128.5[c]	131.3[c]	171.0
		58.3	132.4[c]	127.4[c]	128.3[c]	131.0[c]	170.7
		62.7	131.8[c]	126.9[c]	128.4[c]	130.7[c]	169.5
25[a]	(3.8)	57.3	38.7	27.6			176.6
-100[b]	(3.8x)	57.9	39.1	27.8			175.5

[a] 25 MHz spectrum. [b] 75 MHz spectrum. [c] Tentative assignment. [d] Conformer (3.8) not observed even at -110°C.

Table 3.7 Relative ΔG^{o} (kcal $mole^{-1}$)[a] for Different Conformers of Amides (3.3 - 3.8).

	Imidazolidines		Hexahydropyrimidines			Hexahydro-sym-triazines	
conformer					conformer		
	(3.3)	(3.4)	(3.5)	(3.6)		(3.7)	(3.8)
(a)	1.51	0.35	0.14	0.83	(x)	0.26	0
	(1.18)[c]	(0.09)	(0)	(0.59)		(0)	(0)
(b)	0	0	0	0	(y)	0	[b]
	(0)	(0)	(0.20)	(0)		(0.26)	
(c)	0.76	1.28	0.98	[b]			
	(0.43)	(1.01)	(0.64)				

[a] Calculated using the standard equation $\Delta G^{o} = -RT \ln K$, where K is obtained from the observed relative population ratios. [b] Not observed in NMR. [c] Values given in parenthesis are obtained after compensating for the two distinguishable forms of the conformer (b) in (3.3), (3.4), (3.5) and (3.6) and three indistinguishable forms of the unsymmetrical conformer (y) in (3.7) and (3.8).

In imidazolidines (3.3) and (3.4), (b) was the most stable conformer both before and after compensating for entropy. However, the relative stability of conformers (a) and (c) became interchanged on going from (3.3) to (3.4).

In hexahydropyrimidines (3.5) and (3.6) (b) was the most stable conformer. However, after the correction for entropy in (3.5), (a) becomes the most stable conformer. In (3.6), conformer (c) is not observed at all.

In hexahydro-sym-triazine (3.7) (y) was the most stable conformer, but after compensating for entropy, (x) became the most stable conformer. In (3.8) conformer (y) was not observed at all.

In conclusion, the conformer in which the two tert-butyl groups were on the same side became either the least stable conformer or was not observed at all.

The free energy of activation ($\Delta G^{\neq}$), for the barrier to rotation around the amide C(O)-N bonds, was calculated from the coalescence temperature observed in the ^{1}H NMR spectra, for the methylene protons ($N-CH_2-N$) (table 3.8). All the amides showed only one coalescence temperature, except for compound (3.8) which showed only one conformer even at very low temperature (-110°C).

Table 3.8 Coalescence Temperatures and Free Energies of Activation of Amides (3.3 - 3.8).

Amide	Δ ν (observed exchange in $N-CH_2-N$)		Coalescence[a] temperature (T_c)	Δ $G^{\neq}$ (kcal $mole^{-1}$) Rotational Barrier[b]
(3.3)	(a)-(b)	66	303	14.7
	(b)-(c)	84		14.6
(3.4)	(a)-(b)	33	248	12.3
	(b)-(c)	45		12.2
(3.5)	(a)-(b)	48	298	14.7
	(b)-(c)	111		14.2
(3.6)[c]	(a)-(b)	12	177	9.0
	(b)-(c)	-		-
(3.7)	(x)-(y)	36	263	13.0
		99		12.5
(3.8)[d]		-	-	-

a Only one coalescence temperature was observed.

b Calculated using the equation

$$\Delta G^{\neq}/RT_c = 22.96 + \log_e(T_c/\Delta \nu)$$

c Only two conformers (a) and (b) were observed.

d Only one conformer (x) was observed.

Since imidazolidines and hexahydropyrimidines have three conformers, two $\Delta\nu$ values were obtained (one between conformers (a) and (b) and the other between (b) and (c)) and hence two free energies of activation were obtained for each of the amides. Both values differed by $\pm$ 0.5 kcal $mole^{-1}$.

For hexahydro-sym-triazine (3.7) four signals were seen for the two conformers. The three equal intensity signals at 5.26, 5.37 and 5.71 ppm were assigned to conformer (y) and the remaining signal at 5.38 ppm was assigned to conformer (x) (see Table 3.3). The signal at 5.37 and 5.38 ppm were almost the same, hence for the conversion of (x) to (y) two $\Delta\nu$ values were obtained (one between 5.26 and 5.38 ppm and the other between 5.71 and 5.38 ppm). The two calculated free energies of activation differed by $\pm$ 0.5 kcal $mole^{-1}$.

The benzamides had higher free energies of activation than the corresponding pivalamides. The free energy of activation for 1,3,5-tribenzoylhexahydro-sym-triazine (3.7) was lower (by 2 kcal $mole^{-1}$) than that for the benzoyl derivatives of imidazolidine (3.3) and hexahydropyrimidine (3.5). This decrease in activation barrier might possibly be due to less energetic rotation processes (discussed in section 3.2.10).

3.2.10. Mechanism of Conformer Interconversion

Amides interconvert by bond rotation, and the interconversion pathway is unambiguous for monoamides with only two conformers. However, there has been no mention in the literature about the two possible directions of rotation for the conformer interconversion, clockwise or anticlockwise. This possibility becomes relevant when a chiral center is present, either at the α position to the nitrogen or carbonyl group, or when more than one amide group is present, such as peptides where the sequence (individual or concerted) of rotation about the different amide C(O)-N bonds also becomes an important factor.

Compounds like N-acyl-2-substituted saturated heterocyclic amines [72CC788, 78JCS(P2)1157, 67CB3397, 75BCSJ553, 77BP1465, 83CJC2572] and 1,3,5-trinitroso-sym-triazine [78JMR131] have been investigated by DNMR. However, there has been no mention of the clockwise or anticlockwise rotation of the amide C(O)-N and the nitroso N-N bonds, respectively.

From band shape analysis of the exchange broadened spectra of 1,4-dinitrosopiperazine, cis-2,6-dimethyl-1,4-dinitrosopiperazine, trans-2,5-dimethyl-1,4-dinitrosopiperazine and 1,3,5-trinitrosohexahydro-sym-triazine, the possibility of correlated two bond rotations

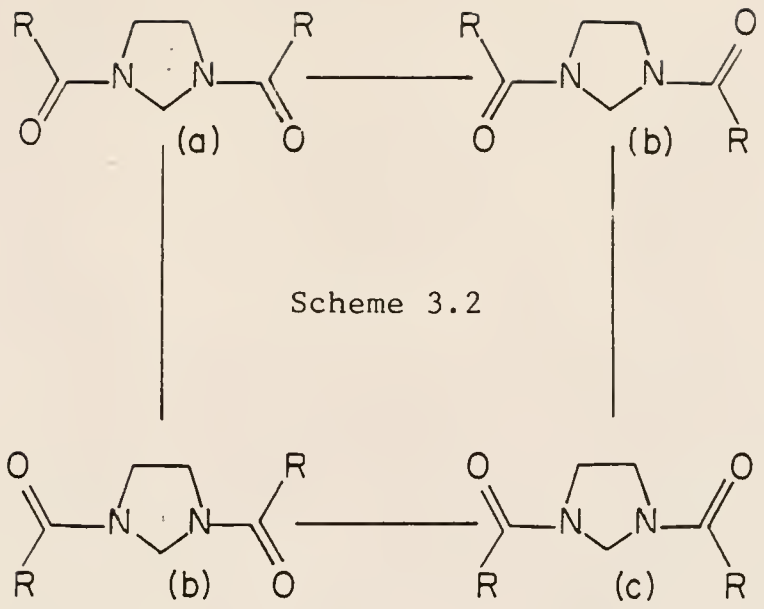
has been excluded, and the spectra have been found to be consistent with the exclusive operation of sequential processes [78JMR131].

Correlated rotations have been found to be the favorable process in triphenylmethyl cations [68JAM4679], in certain substituted [2.2.2.2]paracyclophanetetraenes [84TL4787] and in triarylboranes, methanes and amines [76ACR26].

In triaryl cations, the most favorable mechanism for interconversion of propeller conformers has been proposed to be the three ring flip [68JAM4679]. In triaryl boranes, methanes and amines, of all the possible rotations the favorable and the lowest energy rotation has been found theoretically to be the two ring flip, in which two rings rotate in one direction while the third rotates in the opposite direction [76ACR26].

For the amides (3.3-3.8) with more than two conformers the rotations around the amide C(O)-N bonds could either be; (A) individual (sequential), or (B) concerted (correlated) [78JMR131].

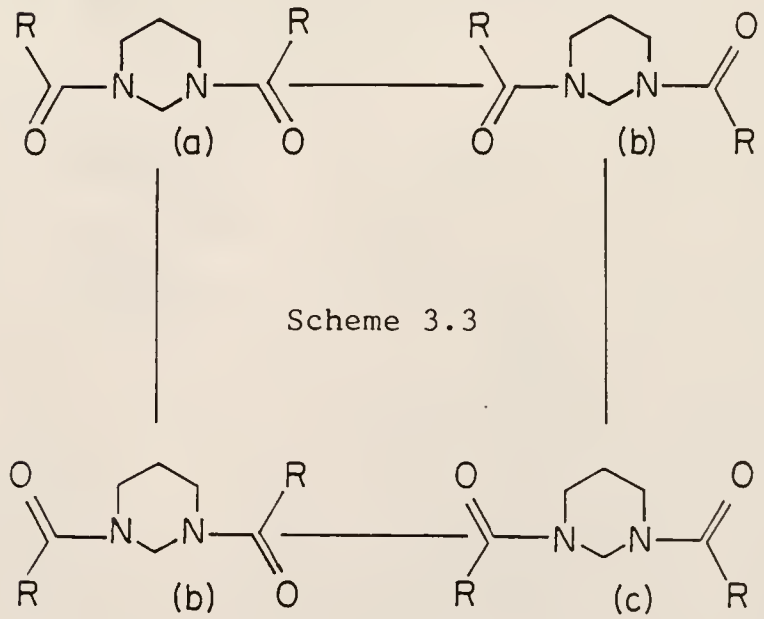
Compounds (3.3), (3.4), (3.5) and (3.6) can exist in three distinct conformers (a), (b) and (c) (scheme 3.2 and 3.3). For each of these amides, mechanism (A) (going along the sides of the square) interconverts conformers (a) and



Scheme 3.2

(3·3) R = C_6H_5

(3·4) R = $C(CH_3)_3$



Scheme 3.3

(3·5) R = C_6H_5

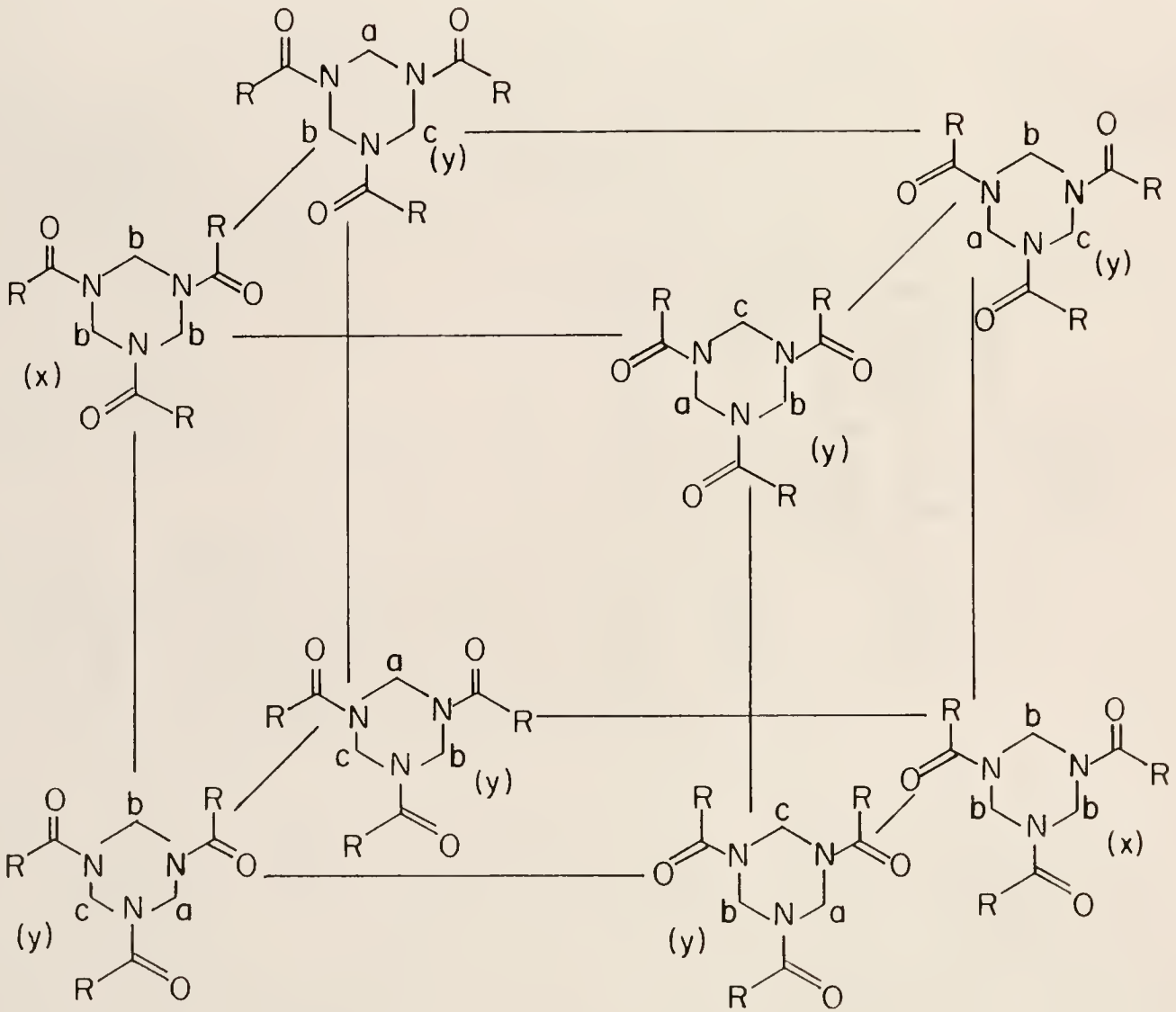
(3·6) R = $C(CH_3)_3$

(b), and conformers (b) and (c), but not directly (a) to (c). On the contrary, mechanism (B) (going along the diagonal of the square) directly interconverts (a) and (c), whereas (b) interconverts only with its topomer [71AG(E)570].

For the tris-amides (3.7) and (3.8) (scheme 3.4), mechanism (A) (going along the sides of the cube) interconverts conformers (x) and (y), as well as changing conformer (y) into its topomers. Mechanism (B) has two possibilities. Firstly, when two amide bonds rotate and the third does not (going along the diagonal of the faces of the cube). This interconverts conformers (x) and (y) as well as changing conformer (y) into its topomers. Secondly, when all three amide bonds rotate (going along the diagonal of the cube). In this case both (x) and (y) merely change into their corresponding topomers [71AG(E)570] (scheme 3.4).

At higher temperatures, fast rotation around the amide C-N bonds should lead to a singlet in the ^{1}H NMR spectrum, for each methylene between two hetero atoms in the ring, irregardless of whether mechanism (A) or (B) is operating.

Higher temperature spectra indeed showed singlets for the C-2 methylene protons of (3.3), (3.4), (3.5) and (3.6). Similarly, the C-2, C-4 and C-6 methylene protons gave one singlet for (3.7) and for (3.8).



(3·7) R = C_6H_5

(3·8) R = $C(CH_3)_3$

Scheme 3.4

As the temperature was lowered, these CH_2 signals for (3.3-3.7) broadened, coalesced and separated as expected into two or more peaks. Surprisingly, the signal for compound (3.8) remained as a singlet even at -110°C.

Thus it can be assumed that in compound (3.8) the rotations around the amide C(O)-N bonds could be correlated, that is, all three amide bonds rotate simultaneously. However, the possiblity of three sequential rotations with conformer (y) as a short lived intermediate in the transitory state can not be ruled out. The two ring flip mechanism [76ACR26] as seen in R_3Z compounds, where Z represents either B, CH or N, and R represents aryl groups, can be extended to compound (3.8) where R represents the pivaloyl group and Z represents the hexahydro-sym-triazine group.

Since DNMR spectroscopy deals exclusively with the phenomenon of site exchange among nuclei, and is uninformative with respect to intermediate states, the information about transitory states can not be obtained. However, for the present system it can be extrapolated from, results that have been obtained on triaryl boranes using molecular mechanics [76ACR26], and simple 1,3-type interactions [68CJC2821].

Considering only simultaneous (correlated) rotations for compounds (3.3), (3.4),(3.5) and (3.6), the rotations around the amide C(O)-N bonds could be either in the same direction or in opposite directions. For conformers (a) and (c) if the rotation is in the same direction then in the transition state the R groups point in the opposite direction. However, if the rotation is in opposite directions then in the transitory state the R groups point in the same direction. Thus from simple 1,3-type interactions [68CJC2821] same side rotations would be favored. For conformer (b) the converse is true, that is opposite side rotations are favored.

On extending similar arguments for the different conformers of compound (3.7) and (3.8), it is obvious that there are three possible ways for the simultaneous rotations: (i) one amide bond in one direction and the other two in the opposite direction, (ii) two amide bonds in one direction and the third in the opposite direction and (iii) all the three amide bonds in one direction, of which (i) and (ii) are essentially the same.

Conformer (x) which is similar to conformer (b) can not rotate in the same direction since all the R groups will point in the same direction in the transitory state which is not a favorable process. Hence it has to go through either

(i) or (ii) which are the same. For conformer (y) however, either of the mechanisms (i) (or (ii)) or (iii) would produce the same transitory state. So conformer (y) can rotate by either of the two possible mechanisms.

3.3. Conclusions

Low temperature ^{1}H and ^{13}C NMR spectra were reported for 1,3-diacylimidazolidines, 1,3-diacylhexahydropyrimidines, and 1,3,5-triacylhexahydro-sym-triazines. Peaks for the individual conformers found were assigned by using model compounds, from relative intensities, and by internal consistencies.

Conformer populations, the energy difference and the energy barrier for their interconversion between them were deduced (Table 3.7 and Table 3.8). A mechanism for their interconversion was proposed.

Conformer populations and the energy difference between the conformers indicate that the conformer in which the two tert-butyl groups point towards each other is the least populated and hence the least stable. This was most pronounced in compounds (3.6) and (3.8) where such a conformer was not observed at all.

All the compounds showed only one coalescence temperature for the N-CH_2-N signal in their ^1H NMR spectra. The free energy of activation for the benzamide was higher than that for the corresponding pivalamides in all the compounds studied.

In conclusion, the mechanism of rotation around the amide bonds in bis- and tris-amides can be sequential or correlated depending upon the interactions that the molecule experiences during the rotation.

3.4. Experimental

3.4.1. Instruments and Methods

Sample solutions for NMR measurements were prepared directly in 5 mm NMR tubes, dissolving approximately 50 mg of the compound in 3-4 mL of the solvent. The solvent used was always $CDCl_3$ except when temperatures lower than -75°C [for (3.6) and (3.8)] were used. In these cases CD_3COCD_3 was used as the solvent. Tetramethylsilane was used as the internal reference. The solvents used for the model systems taken from the literature were either CCl_4 [for (3.13) and (3.14)], $CDCl_3$ [for (3.9), (3.10) and (3.11)] or CH_2Br_2 [for (3.12)].

Room temperature ^{1}H NMR spectra were recorded on a Varian EM 360L spectrometer, and room temperature and high temperature ^{13}C NMR spectra were recorded on a Jeol FX 100 spectrometer. Low temperature ^{1}H and ^{13}C spectra were recorded on a Nicolet NT 300 spectrometer.

3.4.2. Preparation of Amides

The synthesis of saturated heterocyclic amides (3.3), (3.4), (3.5), (3.6), (3.7) and (3.8) was discussed in the experimental part of chapter 2.

CHAPTER 4

HYDROGEN EXCHANGE IN AMIDES

4.1. Introduction

Proton transfer reactions are of extensive academic interest not only for their mechanism but also in the preparation of labelled compounds which are becoming increasingly important in reaction mechanism studies of both chemical and biological systems. While a great deal of attention has been given to carbon acids such as ketones and nitrocompounds [61JAM3688, 63JAM3890, 71JAM2225, 71JAM2231], work on heterocyclic compounds has been less extensive [74AHC1, 73AHC137].

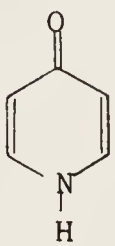
Acid or base catalysed hydrogen exchange is not possible under aqueous conditions with simple amides because they are easily hydrolysed. However, hydrogen exchange in amides can be achieved by the use of strong bases like alkyllithiums followed by quenching with D_2O or CH_3OD [78CR275]. On the other hand, 4-pyridones, which are vinylogous amides, are stable to acids as well as bases and exchange studies on them are possible in aqueous media.

4.1.1. Hydrogen Deuterium Exchange in 4-Pyridones

Hydrogen-deuterium (H/D) exchange can be catalyzed both by acids as well as bases. With N- and O- substituted 4-pyridones both acid [68JCS(B)866, 64RTC186, 67CC1047, 67JCS(B)1226, 68CPB715] as well as base catalyzed [65JAM3365, 64TL3083, 69JOC589] exchanges have been reported. Generally acid catalyzed exchange requires much harsher conditions than the base catalyzed reaction.

4.1.1.1. Acid catalysis of hydrogen exchange in 4-pyridones

Acid catalyzed hydrogen-deuterium exchange occurs at the 3- and 5- positions of 4-pyridones (4.1 - 4.4) at 170°C. 4-Alkoxypyridine (4.5) behave similarly. However, 4-methoxypyridine (4.6) does not exchange under these conditions but undergoes a rearrangement of the methyl group from oxygen to nitrogen [67JCS(B)1226].



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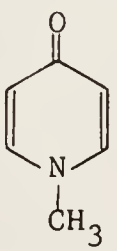

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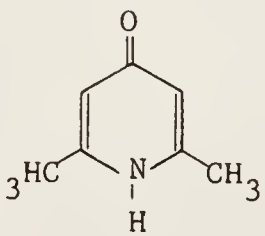

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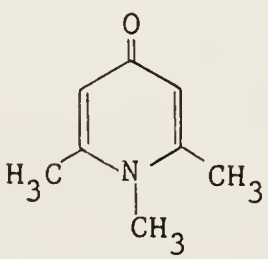

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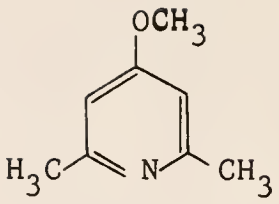

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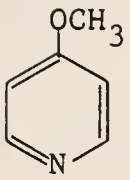

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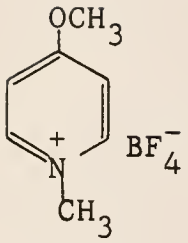


(4.7)

4.1.1.2. Base catalysis of hydrogen exchange in 4-pyridones

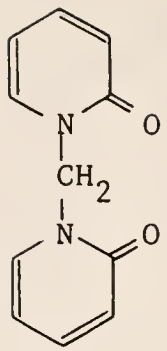
Base catalyzed hydrogen-deuterium exchange, on the other hand, takes place at the 2- and 6- positions of N-alkyl-4-pyridones (4.2) and (4.4) at 100°C and at the same positions of 4-methoxy-1-methylpyridinium tetrafluoroborate (4.7) [65JAM3365, 64TL3083, 69JOC589] at 40°C.

For comparison, the hydrogen-deuterium exchange of the parent system, pyridine, (i) in CH_3OH-CH_3O^- solution at 165°C [69JAM5501], or (ii) in D_2O-OD^- at 200°C [67JAM3358] or (iii) in ND_3-$NaND_2$ at -25°C [68RSO601] displays the reactivity order 2(6) < 3(5) < 4. The least reactivity of the proton adjacent to nitrogen has been ascribed to decrease in s-character of the C2-H bond and to electrostatic repulsion between the coplanar nitrogen and the electron pair of the adjacent anion being formed [69JAM5501]. The effects of halogen substituents in the pyridine ring on the rates of H/D exchange have been studied [66JAM4766]. A halogen at the 3-position accelerates exchange at the 4-position while a halogen at the 4-position accelerates exchange at the 3(5)-positions [74AHC1].

4-Alkoxypyridines are susceptible to alkyl-oxygen cleavage of the alkoxy group by an S_N2 mechanism [69JOC589] and can also undergo isomerization at elevated temperatures to the thermodynamically more stable N-alkyl-4-pyridones [66CC631]. Mechanistic studies of the cleavage of alkyl pyridyl ethers revealed that 4-methoxypyridine (5.6) with CD_3OD-CD_3O^- at 165°C showed exchange at the 3,5-positions of the pyridine ring in addition to the expected ether cleavage [70JOC3462].

4.1.2. Aim of the Work

Further to the investigation of the synergistic effect of amide groups, described in chapter 2, compounds with amide functions in a ring were also considered. Bis(N-2-pyridonyl)methane (4.8) and bis(N-4-pyridonyl)methane (4.9) were chosen for this study. Compound (4.8) was prepared from 2-pyridone and methylene chloride under phase transfer conditions. However, similar reaction with 4-pyridone gave N-(4-pyridinoxymethyl)-4-pyridone (4.10) (Scheme 4.1) instead of (4.9), but compound (4.10) on heating at 200°C rearranged to (4.9). A detailed investigation of the mechanism of this rearrangement is discussed in chapter 5.



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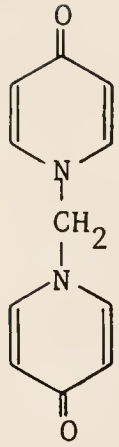

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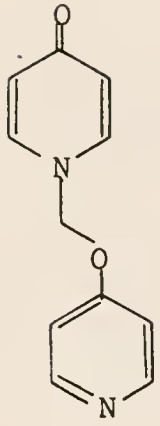
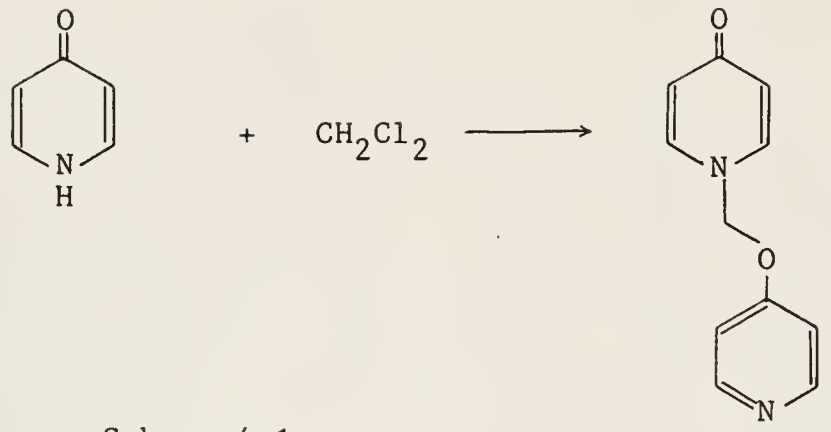


(4.10)

Base catalyzed hydrogen deuterium exchange on these compounds (4.8 - 4.10) was investigated under aqueous conditions since the pyridones were known to be stable to aqueous basic conditions [74MI1]. The exchanges were done in DMSO-d_6 solvent and with NaOD as the base and were followed by ^{1}H NMR. Compound (4.8) showed exchange only at the 6-position of the 2-pyridone rings, similarly (4.9) showed exchange only at the 2,6-positions of the 4-pyridone rings. Interestingly, compound (4.10) showed exchange at pyridine 3,5-positions in addition to the expected exchange at the pyridone 2,6-positions at ambient temperature. However, none of these compounds (4.8 - 4.10) showed any exchange at the N-CH_2-N in (4.8) and (4.9) or at the N-CH_2-O in (4.10) positions.



Scheme 4.1

(4.10)

Although the original objectives were therefore not attained in that the N-CH_2-N groups remained inert, the observation of ambient temperature exchange at pyridine 3,5-positions of compound (4.10) lead to the investigation of the hydrogen-deuterium exchange of various N-substituted 4-pyridones and O-substituted 4-oxypyridines using NMR. In addition there was interest in deuterium labelled substituted pyridines. The main aim of this work was to find out the mechanism of this facile exchange in compound (4.10).

4.2. Results and Discussion

4.2.1. Hydrogen-Deuterium Exchange in N-(4-Pyridinoxymethyl)-4-pyridone

The base catalyzed H,D exchange with NaOD for compound (4.10) was performed in DMSO-d_6. The spectrum of the starting compound (4.10) is shown in Figure 4.1; signal

assignments followed from simple model compounds, multiplicity and coupling constant values. Of the four doublets and a singlet seen the singlet was assigned to the $N-CH_2-O$ protons. The doublets at 6.16 and 7.96 ppm were assigned to the pyridone 3,5 and 2,6 protons, respectively and the doublets at 7.10 and 8.50 ppm were assigned to the pyridine 3,5 and 2,6 protons, respectively. The disappearance of the signal at 7.96 ppm at 25°C showed the expected exchange at the 2,6-positions of the pyridone (Figure 4.2). For N-methyl-4-pyridone similar exchange at pyridone 2,6-positions has been reported at 100°C [65JAM3365]. On warming up to 30-40°C the signal at 7.10 ppm began to decrease in intensity indicating an exchange at the 3- and 5- positions of the pyridine ring (Figure 4.3). For 4-methoxypyridine similar exchange at pyridine 3,5-positions has been reported at 165°C [70JOC3462]. No further exchange was observed either on continuing at this temperature or on further increase in the temperature.

The fact that 4-methoxypyridine does not show exchange of the 3,5-positions at ambient temperature [70JOC3462], suggests that the exchange might be proceeding either by an inter- or intramolecular abstraction of the proton by the anion formed at the pyridone 2(6) position.

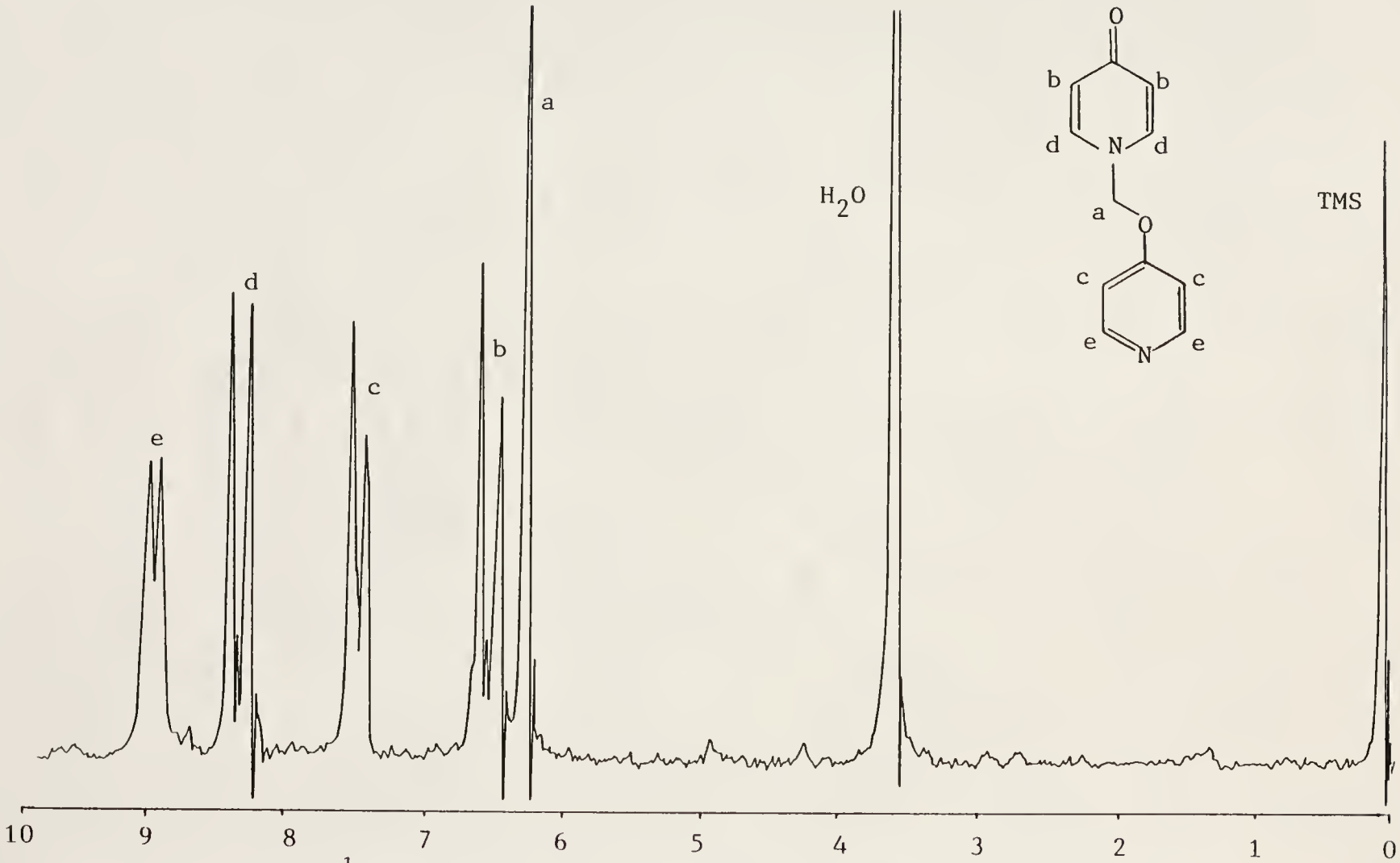


Fig. 4.1 60 MHz ^1H NMR Spectrum of N-(4-Pyridinoxymethyl)-4-pyridone (in DMSO-d_6)

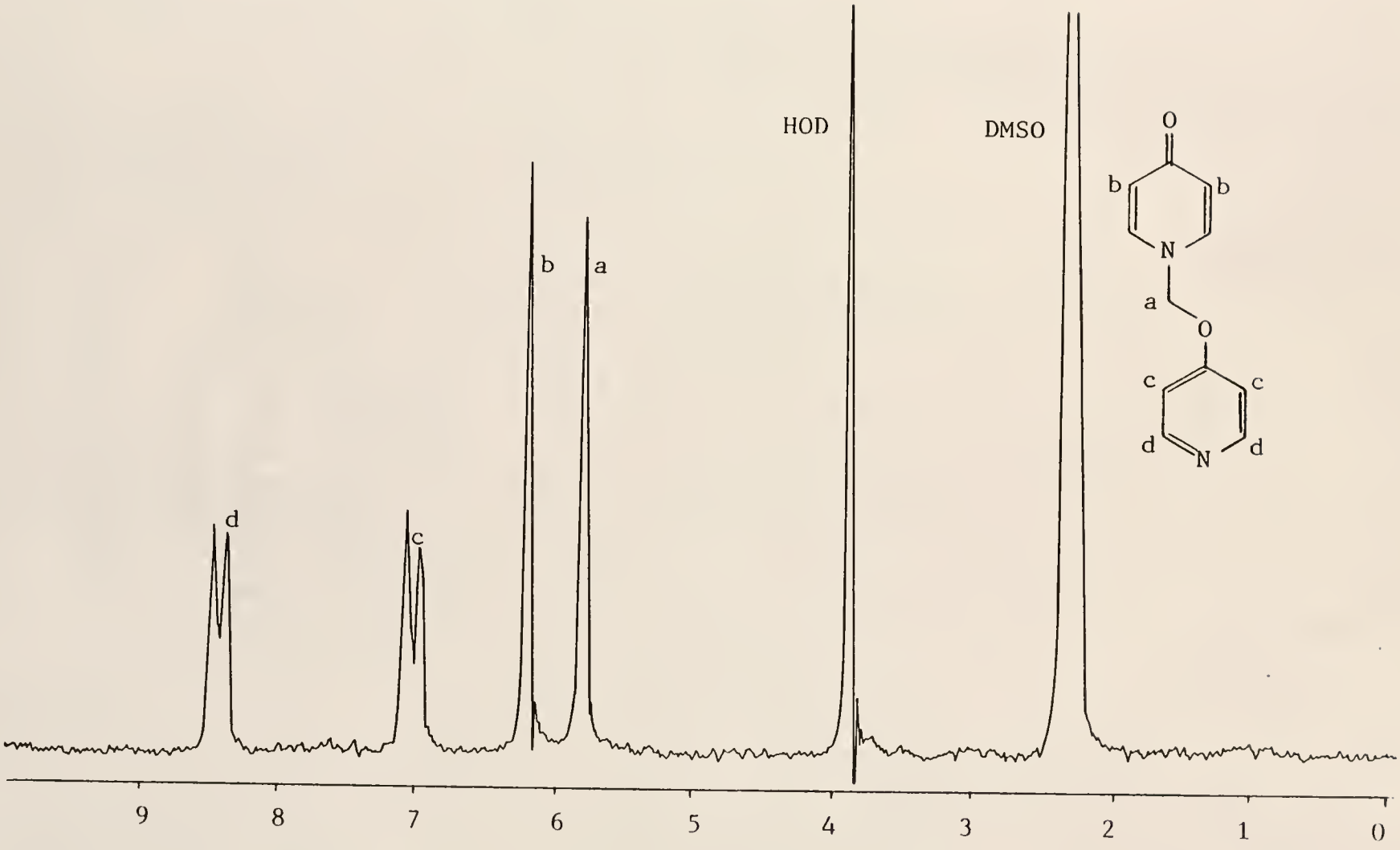


Fig. 60 MHz ^{1}H NMR Spectrum of N-(4-Pyridinoxymethyl)-4-pyridone (in NaOD-DMSO-d_6) After Exchange at 25°c.

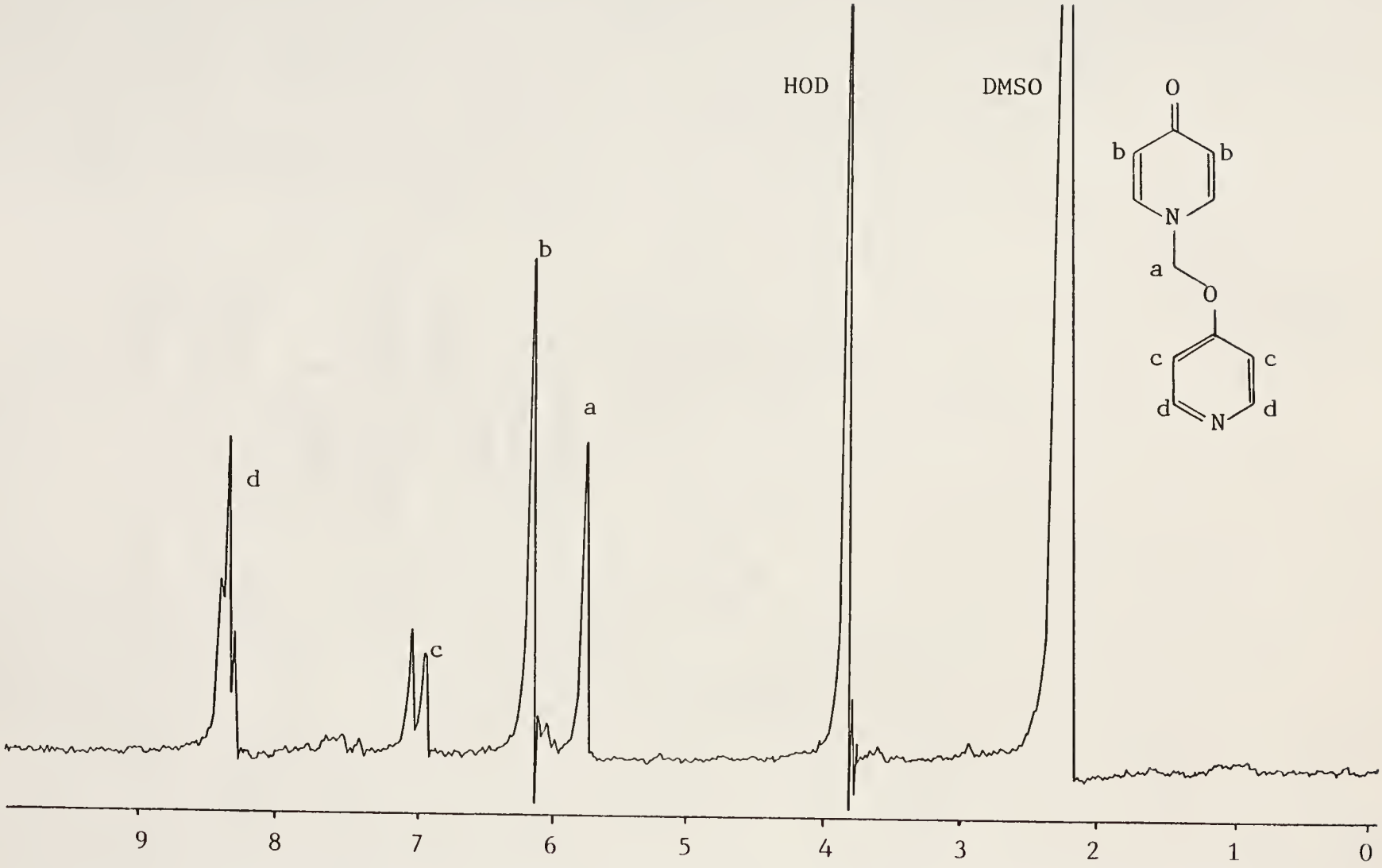
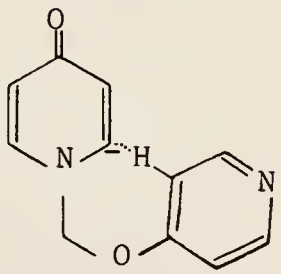
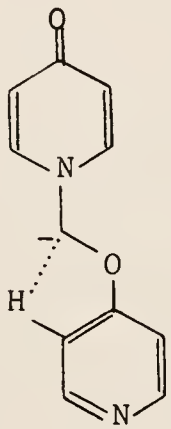


Fig. 3 60 MHz ^{1}H NMR Spectrum of N-(4-Pyridinoxymethyl)-4-pyridone (in NaOD-DMSO-d_6) After Exchange at 40°C.

So it was believed that the base catalysed H/D exchange of compound (4.10) could have happened through either: (i) an intramolecular seven-membered intermediate (4.11), or (ii) an intramolecular five-membered intermediate (4.12), or (iii) a direct abstraction of proton by simple inductive effect similar to that observed for chloropyridines [66JAM4766] and 4-methoxypyridine [70JOC3462]. In case (iii), the direct abstraction of proton may be caused either with an increased inductive electron withdrawing or a decrease in mesomeric electron donation by oxygen.



(4.11)



(4.12)

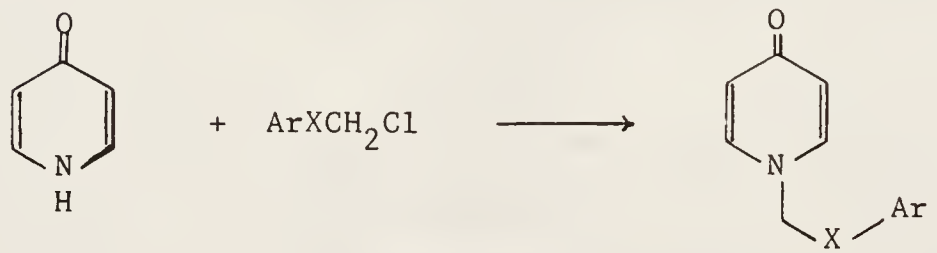
The five-membered intermediate (4.12) was ruled out on the basis that no exchange was observed at the $N-CH_2-O$ methylene protons of (4.10). The same was found to be true for the H/D exchange behavior on different model systems to test (ii) as discussed later in this chapter.

The seven-membered cyclic intermediate of (i) seemed unlikely because with four sp^2 hybridized atoms there will be a severe strain in the ring, also entropy does not favor this intermediate (4.11).

However, model compounds were prepared to test all the three possible mechanisms (i), (ii) and (iii).

4.2.2. Hydrogen-Deuterium Exchange in N-(Phenoxymethyl)-4-pyridone and N-(Arylthiomethyl)-4-pyridones

To test mechanisms (i) and (ii), N-(phenoxymethyl)-4-pyridone (4.13) and N-(4-methylthiophenylmethyl)-4-pyridone (4.14), were prepared from 4-pyridone and chloromethylphenyl ether and 4-pyridone and chloromethyl-(4-methylphenyl) sulfide, respectively (scheme 4.2).



Scheme 4.2

(4.13) Ar = C_6H_5 X = O

(4.14) Ar = 4-$CH_3C_6H_4$ X = S

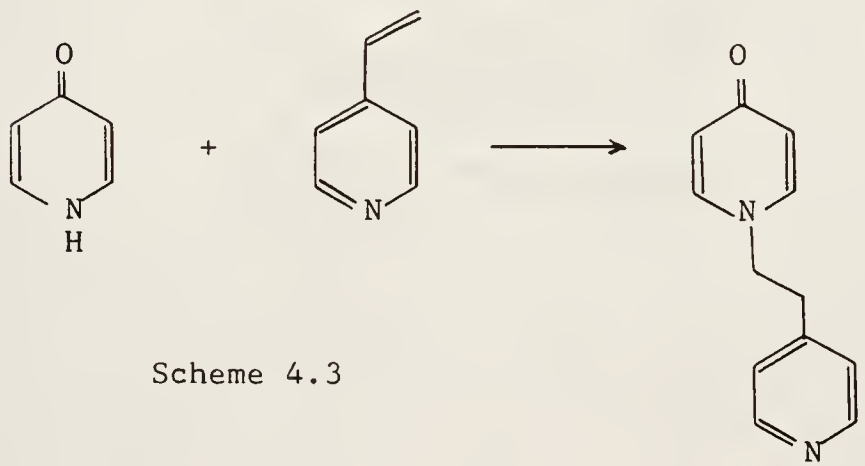
(4.15) Ar = 4-$NO_2C_6H_4$ X = S

Hydrogen-deuterium exchange studies on (4.13) followed by ^{1}H NMR showed, as expected, exchange at the 2,6-hydrogens of the pyridone ring at 25°C. On increasing the temperature to 50°C or more no exchange in the phenyl ring hydrogens was observed. Similarly hydrogen-deuterium exchange of (4.14) occurred as expected at the methylene hydrogens at 25°C and on warming up to 40°C the 2,6-hydrogens of the pyridone ring also exchanged. Prolonged heating at this temperature or increasing the temperature did not show any exchange in the 4-methylphenyl ring hydrogens.

This lead to the belief that the aryl ring has to be a pyridine ring in order for an exchange to occur. Thus a study of the hydrogen-deuterium exchange behavior of N-(4-nitrophenylthiomethyl)-4-pyridone (4.15) was attempted in which we expect the 4-nitrophenyl ring to behave like the 4-pyridyl ring. Compound (4.15) was prepared from 4-pyridone and chloromethyl (4-nitrophenyl) sulfide (scheme 4.2). However, compound (4.15) on H/D exchange in DMSO-d_6 and NaOD and followed by ^{1}H NMR, showed signal broadening. This was due to the radical anion formed by an aromatic nitro compound in the presence of a carbanion as has been reported in the literature [66JOC248]. The formation of a dark red color together with the disappearance of the methylene

singlet and the reduction in the intensity of the pyridone 2,6-proton signal indicated exchange at these sites. The 4-nitrophenylthio group being a better leaving group, on continuing the exchange, the compound underwent S_N2 displacement, and 4-nitrophenyl thiol was isolated from the reaction mixture.

Hence N-(4-pyridylethyl)-4-pyridone (4.16) was prepared from 4-pyridone and 4-vinylpyridine (scheme 4.3) in order to test mechanism (i). However, compound (4.16) in DMSO-d_6 on treatment with NaOD and followed by ^{1}H NMR showed the aliphatic CH_2-CH_2 signals to disappear and vinylic signals began to appear and they increased in intensity with time. This indicated that the starting materials were formed as has been observed for similar N-protected compounds [84TL1223].



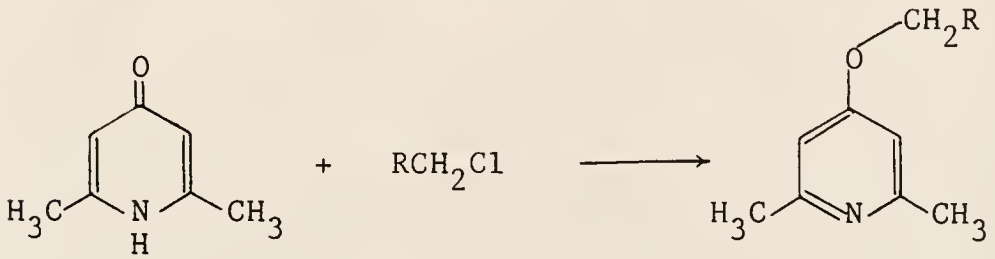
Scheme 4.3

(4.16)

4.2.3. Hydrogen-Deuterium Exchange in 2,6-Dimethyl-4-alkoxypyridine Model Compounds

In order to test mechanism (iii) and (ii) 4-benzoylmethoxy-2,6-dimethyl-4-pyridone (4.17) and bis(2,6-dimethyl-4-pyridinoxy)methane (4.18) were prepared.

Compound (4.17) was prepared from α-bromoacetophenone and 2,6-dimethyl-4-pyridone and compound (4.18) from 2,6-dimethyl-4-pyridone and methylene chloride under phase transfer conditions (scheme 4.4).



Scheme 4.4

(4.17) R = C_6H_5CO-

(4.18) R = 4-(2,6-Di-methylpyridinoxy)-

Compound (4.17) in DMSO-d_6 and NaOD and followed by ^1H NMR showed exchange only at the methylene protons and continuing the exchange led to the S_N2 displacement of the 2,6-dimethyl-4-pyridone. Compound (4.18) was found to be stable under these conditions. However, no exchange at the pyridine 3,5-positions was observed; on prolonging the conditions for a long time, the methyl groups began to show an exchange.

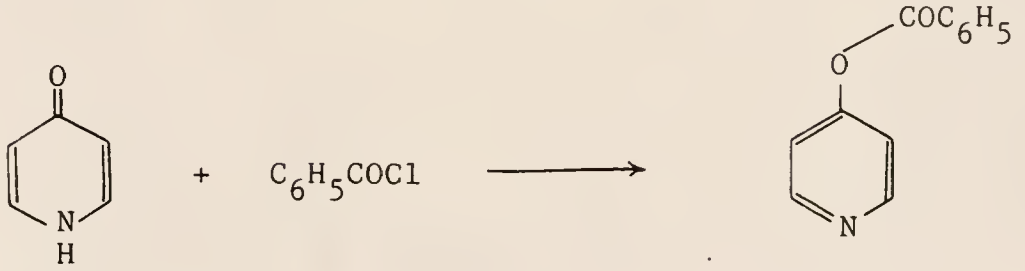
A drawback in these model systems was that though the pyridine ring was present, the methyl groups present at the 2,6-positions may retard the exchange, as has been observed in exchange studies with 3-substituted pyridines [74JCS(P2)1363]. As a result, model systems without 2,6-methyl groups in the pyridine ring were considered.

4.2.4. Hydrogen-Deuterium Exchange in 4-Alkoxypyridine Model Compounds

In order to test mechanism (iii), with an increase in the inductive electron withdrawal or a decrease in the mesomeric electron donation by oxygen, the following model compounds were prepared. 4-Pyridyl benzoate (4.19) and 4-phenoxypyridine (4.20) mainly with an increase in the electron withdrawal by oxygen, due to the resonance effect happening in the opposite direction with the carbonyl and a phenyl group, respectively. And 2-(4-pyridinoxy)ethanol (4.21) and 4-(2-aminophenoxy)pyridine (4.22) mainly with a decrease in the mesomeric electron donation by oxygen, due to an intramolecular hydrogen bonding between the -OH and oxygen and $-NH_2$ and oxygen, respectively.

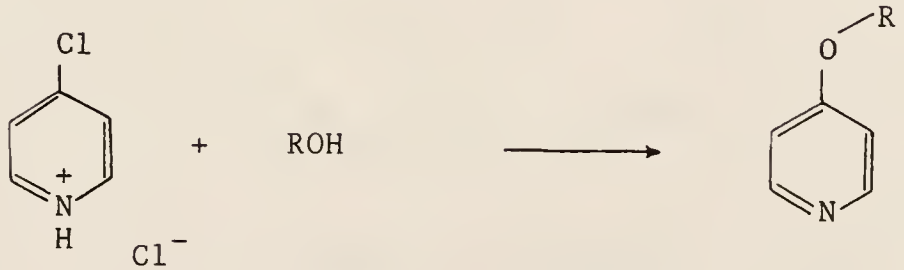
Compound (4.19) was prepared from 4-pyridone and benzoyl chloride (scheme 4.5) and compound (4.20) from 4-chloropyridine hydrochloride and phenol (scheme 4.6).

4-Pyridyl benzoate (4.19) in DMSO-d_6 and NaOD and followed by ^1H NMR showed hydrolysis while 4-phenoxypyridine (4.20) did not show any exchange.



(4.19)

Scheme 4.5



(4.20) R = C_6H_5

(4.21) R = CH_2CH_2OH

(4.22) R = $2\text{-}NH_2C_6H_4$

Scheme 4.6

Compound (4.21) was prepared from 4-chloropyridine hydrochloride and ethylene glycol and compound (4.22) was prepared similarly from 4-chloropyridine hydrochloride and 2-aminophenol (scheme 4.6).

The ^{1}H NMR spectrum of 2-(4-pyridinoxy)ethanol (4.21) in DMSO-d_6 showed a multiplet between 3.70-4.30 ppm for the CH_2-CH_2 protons and a broad signal at 4.35 ppm for -OH. The doublet at 7.10 ppm and a broad singlet at 8.55 ppm were assigned to the pyridine 3,5- and 2,6-protons, respectively (Figure 4.4). On adding CD_3ONa the multiplet between 3.70-4.30 ppm narrowed, the signal at 8.55 ppm became a doublet (indicating that in neutral solution for (4.21) the acidic -OH proton is equilibrating between the hydroxyl oxygen and the nitrogen) and as expected the broad singlet at 4.35 ppm disappeared (Figure 4.5). On increasing the temperature the aliphatic multiplet began to disappear and a new aliphatic singlet peak began to appear indicating the ether cleavage of (4.21) and formation of ethylene glycol. However, at 85°C the doublet at 7.10 ppm began to decrease in intensity with an increase in intensity of the signal at 8.55 ppm indicating the exchange at pyridine 3,5-positions (Figure 4.6).

4-(2-Aminophenoxy)pyridine (4.22) (Figure 4.7) in CD_3ONa/CD_3OD/DMSO-d_6 and followed by ^{1}H NMR showed a decrease in intensity of the pyridine 3,5-protons signal with an increase in the signal intensity of the pyridine 2,6-protons (Figure 4.8). This indicated an exchange at the pyridine 3,5-positions. The expected ether cleavage

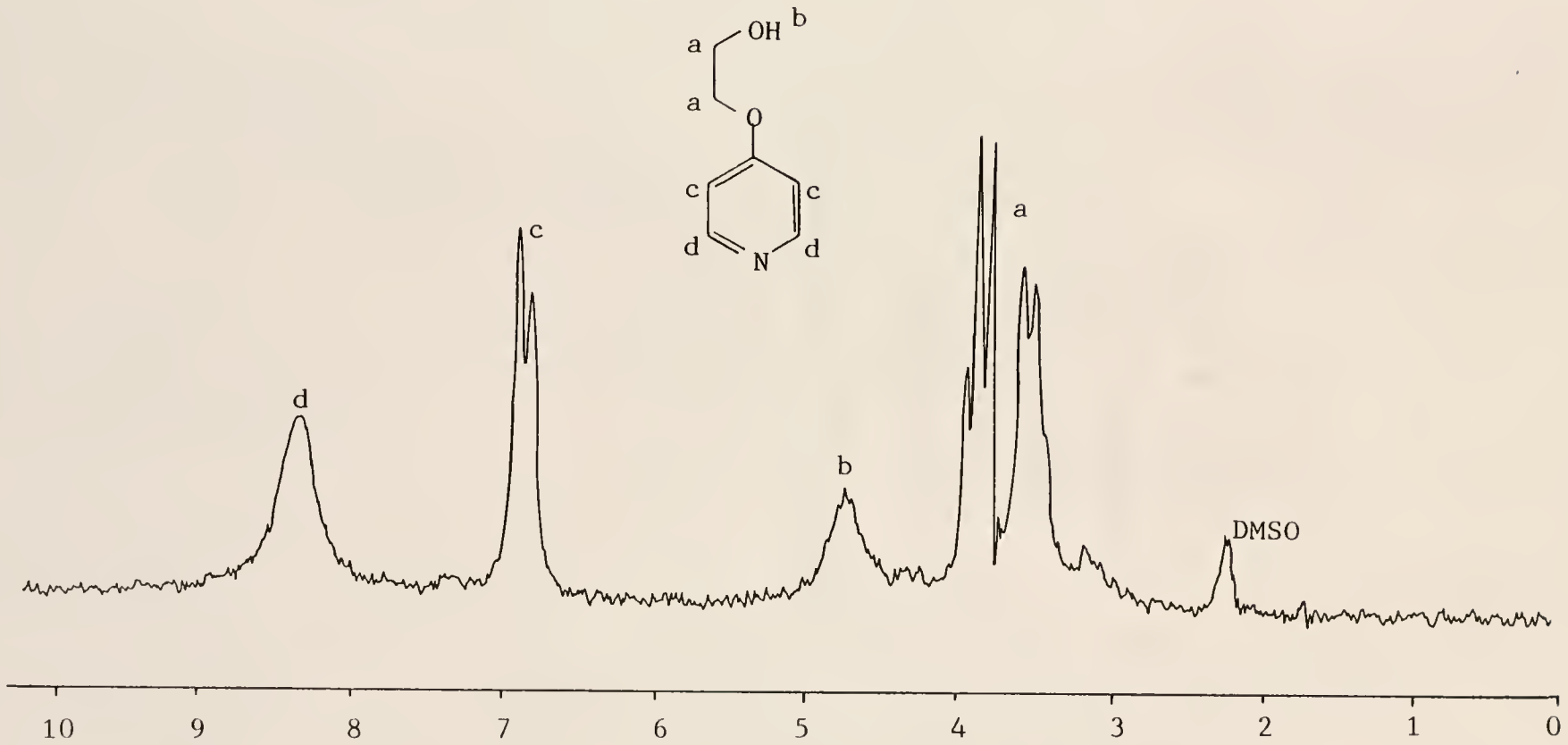


Fig. 4.4 60 MHz ^{1}H NMR Spectrum of 2-(4-Pyridinoxy)ethanol (in DMSO-d_6).

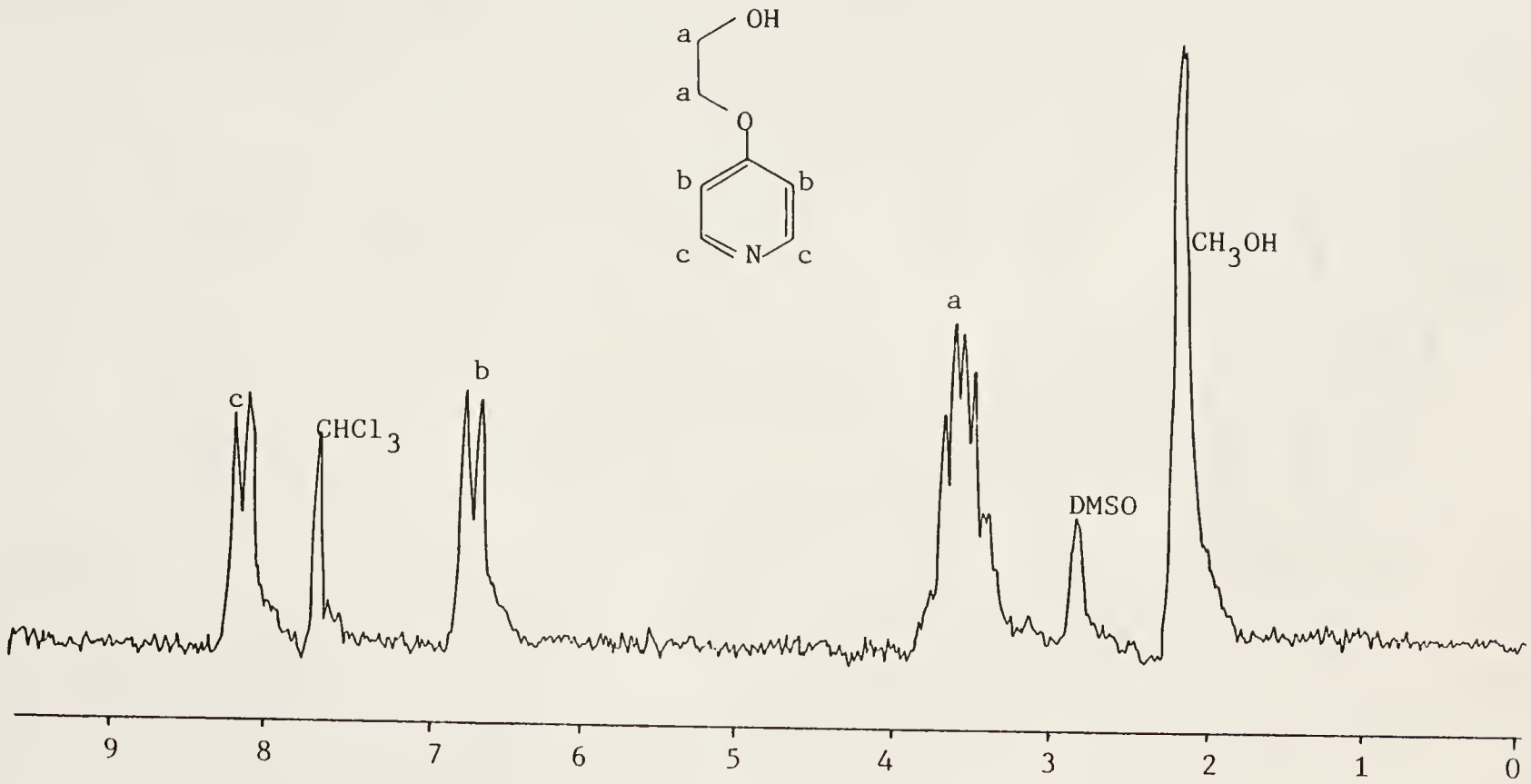


Fig. 5 60 MHz ^{1}H NMR Spectrum of 2-(4-Pyridinoxy)ethanol (in CD_3ONa-CD_3OD-DMSO-d_6) at 25°C.

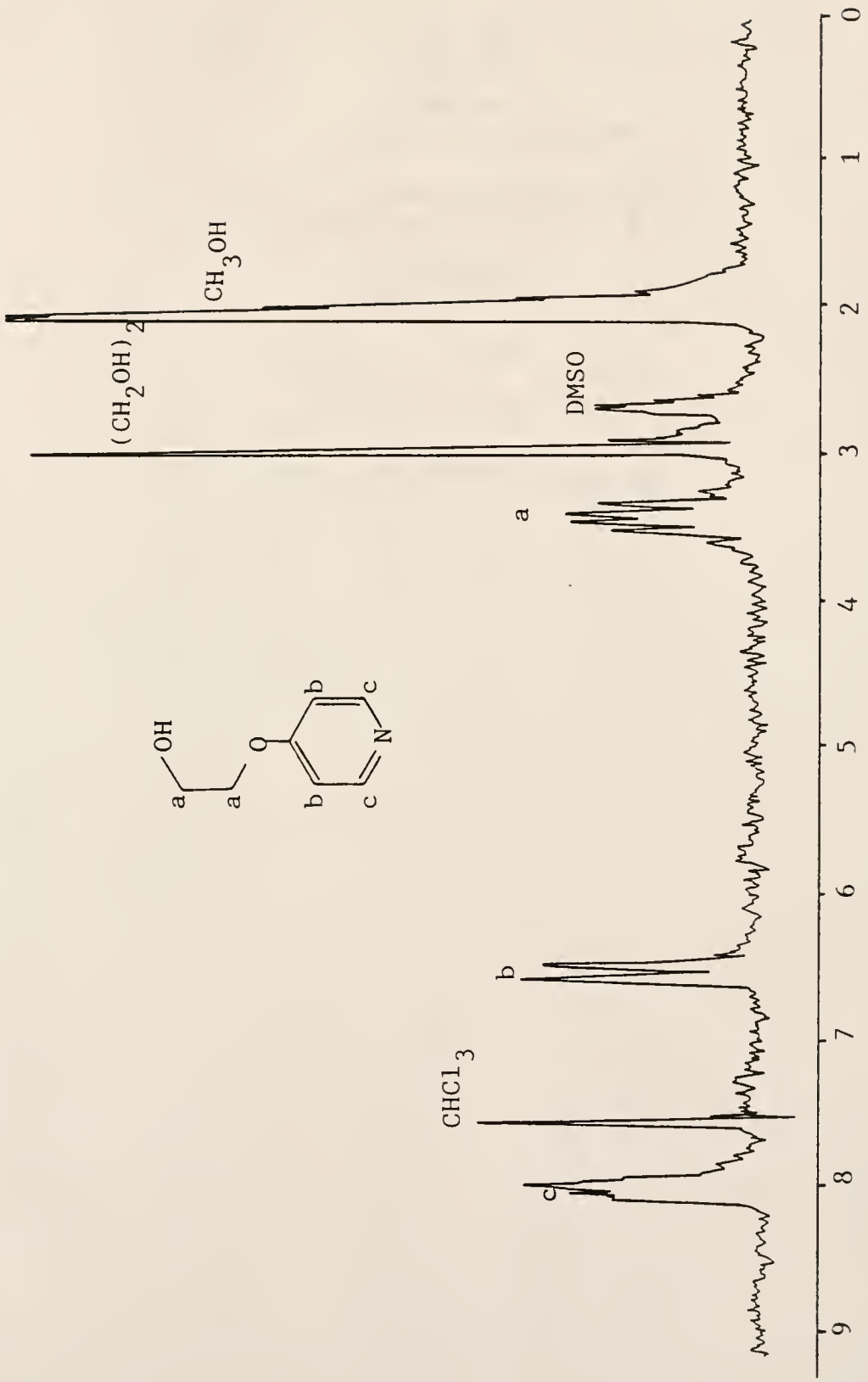


Fig. 60 MHz ^{1}H NMR Spectrum of 2-(4-Pyridinoxy)ethanol (in CD_3ONa-CD_3ONa-DMSO-d_6) After Exchange at 70°C.

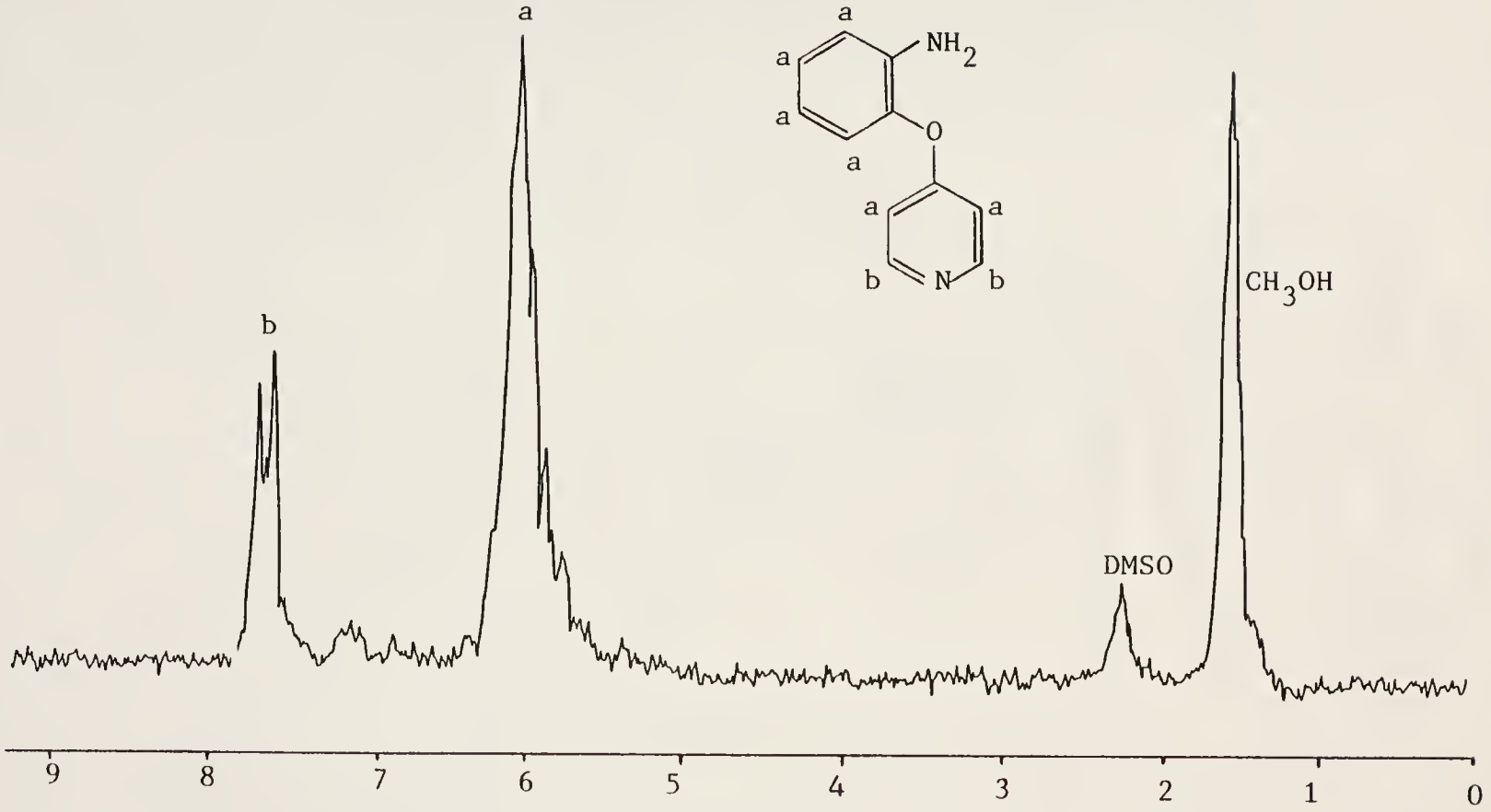


Fig. 4.7 60 MHz ^{1}H NMR Spectrum of 4-(2-Aminophenoxy)pyridine (in CD_3ONa-DMSO-d_6).

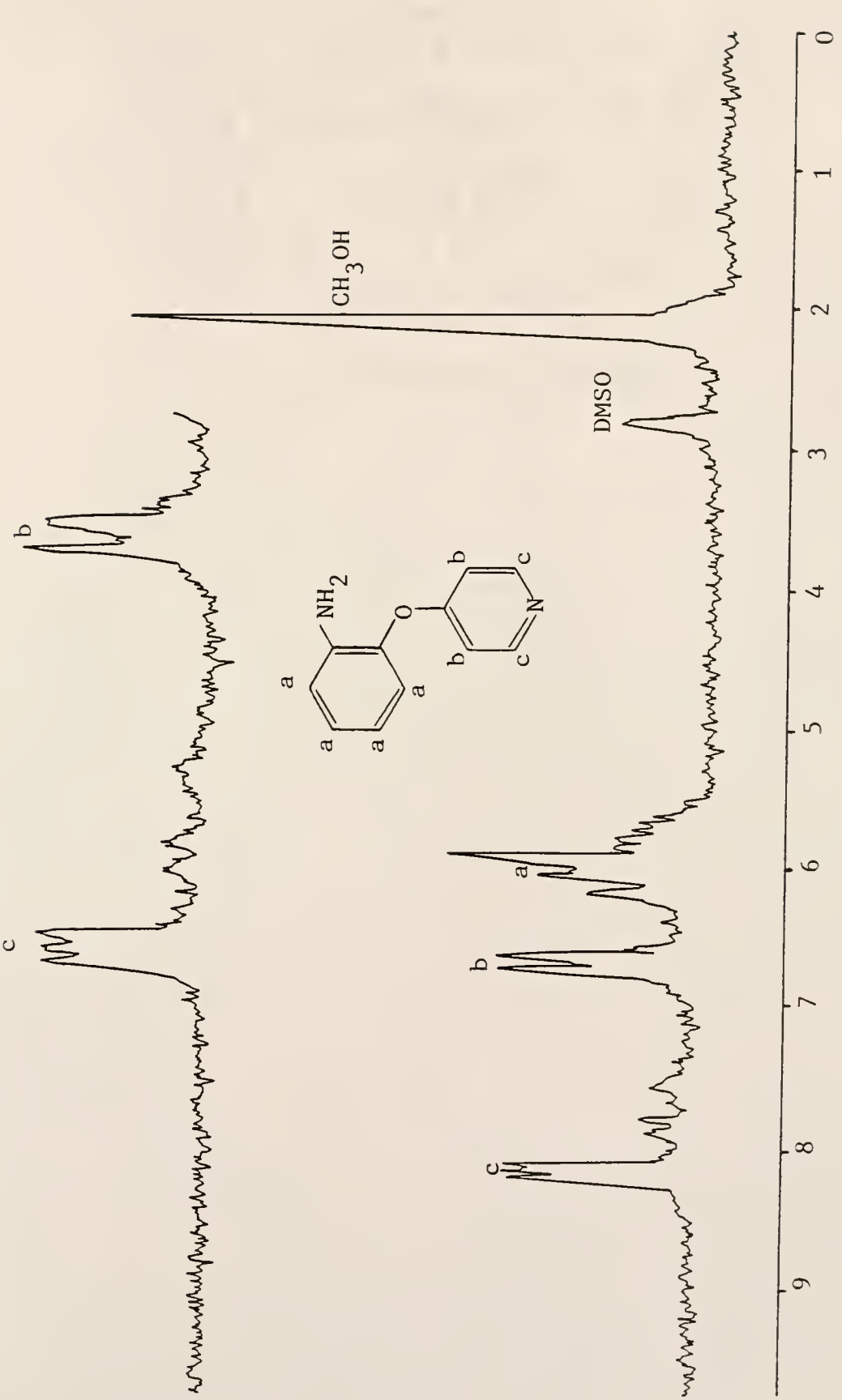
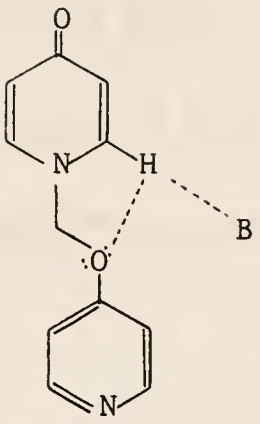


Fig. 3 60 MHz ^1H NMR Spectrum of 4-(2-Aminophenoxy)pyridine (in CD_3ONa-$DMSO-d_6$) After Exchange at 70°C.

reaction was also observed here. This observation of exchange at pyridine 3,5-positions with compounds (4.21) and (4.22) was similar to that observed for compound (4.10) (at 35-40°C) but at a higher temperature (85°C).

This observation led to the conclusion that in compound (4.10) the exchange at the pyridine 3,5-positions was proceeding by mechanism (i). The fact that 4-methoxypyridine did not show any exchange similar to (4.10), (4.21) and (4.22) showed that there was an interaction between the lone pair on oxygen attached to the pyridine ring and the easily exchangeable proton at the γ-position of the O-substituent.

Experimental evidence for the assistance by the oxygen for the proton removal was obtained by comparing the hydrogen-deuterium exchange behavior of compound (4.10) and N-methyl-4-pyridone (4.2) [65JAM3365] under identical conditions. Compound (4.10) was found to exchange in DMSO-d_6 and NaOD five times faster than (4.2). Hence in the exchange of compound (4.10) the effect has to be an enhanced inductive electron withdrawal by oxygen and the transition state involved may be as shown in (4.23).



(4.23)

4.3. Conclusions

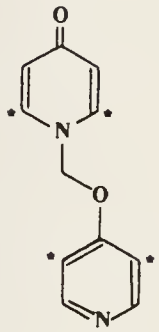
From the results obtained for the base catalyzed hydrogen deuterium exchange behavior of N-substituted 4-pyridones and O-substituted 4-oxypyridines (Figure 4.9) the following points can be said:

(1) A heteroatom at the β-position of the N-alkyl substitution enhances the H/D exchange rate for the 2,6-positions in N-alkyl-4-pyridones.

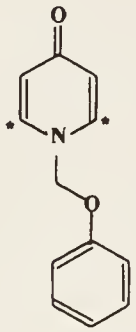
(2) A heteroatom at the γ-position of the O-alkyl substitution with exchangeable hydrogen or a γ-acidic C-H enhances the hydrogen exchange rate for the 3,5-positions in 4-alkoxypyridines.

(3) In general by manipulating the substituents on nitrogen in N-alkyl-4-pyridones and oxygen in 4-oxypyridines base catalyzed hydrogen exchange can be achieved either at the 2,6-positions or at the 3,5-positions at ambient temperatures.

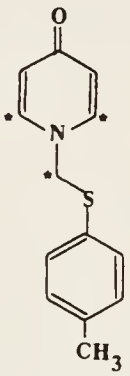
Figure 4.9 Base Catalyzed Hydrogen-Deuterium Exchange in Different N- and O-Substituted 4-Pyridones (the exchanging positions are indicated by * mark)



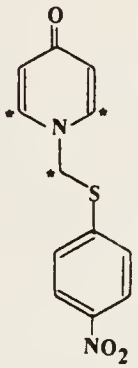
(4.10)



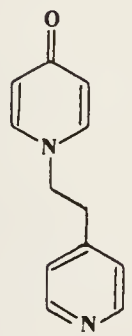
(4.13)



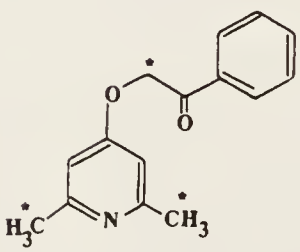
(4.14)



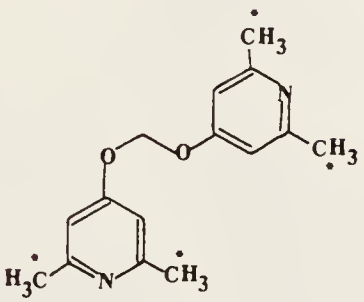
(4.15)



(4.16)



(4.17)



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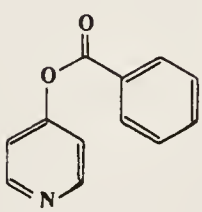

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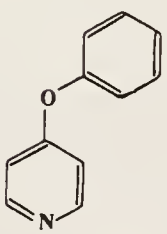
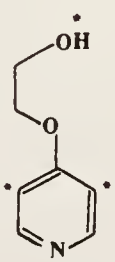
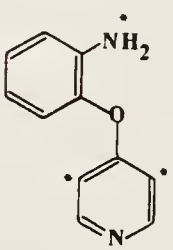


(4.20)



(4.21)



(4.22)

4.4. Experimental

Melting points were recorded on a Bristoline hot-stage microscope and are uncorrected. The ^{1}H NMR spectra were recorded on a Varian 360L spectrometer using TMS as the internal reference and ^{13}C NMR spectra were recorded on a JEOL FX 100 spectrometer and Varian XL 200 spectrometer using the solvent (DMSO-d_6) peak as the reference. The IR spectra were obtained on a Perkin-Elmer 283 B spectrophotometer

4.4.1. Method and Reagents

All hydrogen-deuterium exchanges have been done with excess NaOD (1 M) in dimethylsulfoxide-d_6 as solvent unless indicated. All exchanges were followed using the decrease in the peak intensity of the exchanging proton coupled with the disappearance of the coupling of the exchanging proton with the vicinal proton (^{1}H NMR) and were confirmed with ^{13}C NMR which showed a decrease in signal intensity of the carbon to which the exchanging proton is attached.

General procedure for hydrogen-deuterium exchange: The pyridone (25-30 mg) was taken in a 5 mm NMR tube and was dissolved in 0.3 mL of DMSO-d_6. To this NaOD or CD_3OD

(0.20-0.25 mL, 1 M) was added and the ^1H NMR spectra were recorded periodically. For higher temperature exchange the NMR tubes were heated in an oil bath maintained at the required temperature.

Chloromethyl phenyl ether, b.p. 90-95°C (20mm) (lit.[77CI127], b.p. 87-89°C (16mm)), chloromethyl phenyl sulfide, b.p. 85-90 °C (5mm) (lit.[77JOC3094], b.p. 83°C (1.5mm)), 2,6-dimethyl-4-pyridone, m.p. 224°C (lit.[50JOC337], m.p. 225°C), N-methyl-4-pyridone (4.3), m.p. 95°C (lit.[65JAM3365], m.p. 92-93°C) and 4-pyridylbenzoate (4.19), m.p. 82°C (lit.[59JCS2844], m.p. 79-80°C) were prepared by literature methods. 4-Methoxypyridine (4.6), b.p. 80-85°C (20-25mm) (lit.[68JAM1569], b.p. 80-82°C (15-20mm)), was prepared from 4-methoxypyridine-N-oxide following an analogous procedure [53JOC534]. 4-Pyridone (4.1) and 4-methoxypyridine-N-oxide were obtained from Aldrich.

4.4.2. Preparation of N-(4-Pyridinoxymethyl)-4-pyridone

4-Pyridone (4.75 g 0.05 mole), benzyltriethyl-ammonium chloride (0.57 g 0.0025 mole), potassium carbonate (6.9 g 0.05 mole) and potassium hydroxide (84% 3.5 g) were vigorously stirred and refluxed in methylene chloride (300 mL). After 48 h the CH_2Cl_2 was filtered off, the residue extracted with hot CH_2Cl_2 and combined with the filtrate.

It was dried with anhydrous $MgSO_4$, filtered and the solvent evaporated to give 1.18 g (25%) of (4.10): m.p. 199-201°C; IR ($CHBr_3$) 1650 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.00 (s, 2H), 6.16 (d, 2H, J=8 Hz), 7.10 (d, 2H, J=6 Hz), 7.96 (d, 2H, J=8 Hz), 8.50 (d, 2H, J=6 Hz). Anal. calcd. for $C_{11}H_{10}N_2O_2.H_2O$: C, 60.0; H, 5.5; N, 12.7. Found: C, 60.1; H, 5.6; N, 12.7.

4.4.3. Preparation of N-(Phenoxymethyl)-4-pyridone and N-(Arylthiomethyl)-4-pyridones

Preparation of N-(phenoxymethyl)-4-pyridone (4.13)

4-Pyridone (2.38 g 0.025 mole), benzyltriethyl-ammonium chloride (0.575 g 0.0025 mole), potassium hydroxide (3.6 g 84%) and chloromethyl phenyl ether [81TL1973] (3.56 g 0.025 mole) were vigorously stirred and refluxed in methylene chloride (300 mL). After 48 h CH_2Cl_2 was filtered off and the resude extracted with hot CH_2Cl_2, combined with the filtrate and dried with anhydrous $MgSO_4$. This was then filtered and solvent evaporated to give 2.5 g (50%) of (4.13): m.p. 149-151°C; IR ($CHBr_3$) 1630 cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.90 (s, 2H), 6.25 (d, 2H, J=7 HZ), 7.25 (m, 5H), 7.95 (d, 2H, J=7 Hz). Anal. calcd. for $C_{12}H_{11}NO_2$: C, 71.6; H, 5.5; N, 7.0. Found: C, 71.5; H, 5.6; N, 6.7.

Preparation of N-(4-methylphenylthio)-4-pyridone (4.14)

To a solution of 4-pyridone (2.38 g 0.025 mole) dissolved in absolute ethanol (50 mL), was added sodium (0.58 g 0.025 mole). After the metal had dissolved, 4-methylphenyl chloromethyl sulfide [77JOC3094] (4.31 g 0.025 mole) was added and the mixture refluxed for 12 h. After cooling to 25°C it was poured into water and extracted with chloroform (3x50 mL). The $CHCl_3$ extract was dried with anhydrous $MgSO_4$, filtered and removal of the solvent gave 3.5 g (60%) of (4.14): m.p. 105°C; IR($CHBr_3$) 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.32 (s, 3H), 4.98 (s, 2H), 6.33 (d, 2H, J=9 Hz), 7.10-7.48 (m, 6H). Anal. calcd. for $C_{13}H_{13}NOS$: C, 67.50; H, 5.66; N, 6.06. Found: C, 67.84; H, 5.83; N, 5.96.

Preparation of N-(4-nitrophenylthio)-4-pyridone(4.15)

Prepared following the same procedure as described for (4.14) but using 4-nitrophenyl chloromethyl sulfide [77JOC3094] gave 2.6 g (40%) of (4.15): m.p. 118-120°C; IR($CHBr_3$) 1615, 1525, 1330 cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.80 (s, 2H), 6.18 (d, 2H, J=8 Hz), 7.75-8.10 (m, 4H), 8.45 (d, 2H, J=9 Hz). Anal. calcd. for $C_{12}H_{10}N_2O_3S$: C, 54.90; H, 3.82; N, 10.69. Found C, 54.50; H, 3.83; N, 10.36.

4.4.4. Preparation of N-(4-Pyridylethyl)-4-pyridone (4.16)

4-pyridone (0.95 g 0.01 mole) and 4-vinylpyridine (1.05 g 0.01 mole) taken in 10mL of ethanol were refluxed for 10 h. The reaction mixture was cooled and ether was added to the mixture to give 1.8 g (90%) of compound (4.16): m.p. 78-80°C; IR ($CHBr_3$) 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.12 (t, 2H J=7 Hz), 4.22 (t, 2H J=7 Hz), 6.40 (d, 2H J=7 Hz), 7.22 (d, 2H J=5 Hz), 7.50 (d, 2H J=7 Hz), 8.70 (d, 2H J=5 Hz). Anal. calcd. for $C_{12}H_{12}N_2O$: C, 72.00; H, 6.00; N, 14.00. Found C, 72.12; H, 6.23; N, 13.91.

4.4.5. Preparation of 2,6-Dimethyl-4-alkoxypyridines

Preparation of 2,6-dimethyl-4-pyridyl phenacyl Ether (4.17)

Prepared following the same procedure as described for (4.14) but using phenacyl bromide in place of 4-methylphenyl chloromethyl sulfide, gave 4.5 g (75%) of compound (4.17): m.p. 225°C; IR ($CHBr_3$) 1690 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.80 (s, 6H), 6.20 (s, 2H), 7.68 (s, 2H), 7.75-8.45 (m, 5H). Anal. calcd. for $C_{15}H_{15}NO_2$: C, 74.69; H, 6.22; N, 5.81. Found: C, 74.55; H, 6.48; N, 5.68.

Preparation of bis(2,6-dimethyl-4-pyridinoxy)methane (4.18)

Prepared following the same procedure as described for compound (4.10) but using 2,6-dimethyl-4-pyridone in place of 4-pyridone, gave 5.5 g (85%) of compound (4.18): m.p. 73-75°C; IR ($CHBr_3$) 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.58 (s, 12H), 5.93 (s, 2H), 6.91 (s, 4H). Anal. calcd. for $C_{15}H_{18}N_2O_2$: C, 69.77; H, 6.98; N, 10.85. Found C, 69.55; H, 7.15; N, 10.68.

4.4.6. Preparation of 4-Alkoxypyridine Model Compounds

Preparation of 4-phenoxypyridine (4.20)

4-Chloropyridine hydrochloride (3.0 g 0.02 mole) was dissolved in dimethyl sulfoxide (40 mL) and phenol (1.88 g 0.02 mole) and sodium hydroxide pellets (2.0 g) were added and heated gently at 100°C overnight. The mixture was cooled and poured into ice and water (300 g) and extracted with ether many times until the ether layer is colorless. The ether extracts were all combined and dried with anhydrous magnesium sulfate, filtered and the solvent evaporated, gave 3.0 g (88 %) of compound (4.20):m.p. 45°C (lit.[31CB1049], m.p. 44-46°C); IR ($CHBr_3$) 1230 cm^{-1}; ^1H NMR($CDCl_3$) δ 6.60-7.50 (m, 7H), 8.50 (d, 2H J=5 Hz). Anal. calcd. for $C_{11}H_9NO$: C, 77.19; H, 5.26; N, 8.19. Found: C, 77.52; H, 5.31; N, 8.12.

Preparation of 2-(4-pyridinoxy)ethanol (4.21)

The same procedure as described above for compound (4.20) except phenol was replaced by ethylene glycol, gave 2.0 g (72 %) of compound (4.21): m.p. 118-120°C; IR ($CHBr_3$) 3650 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.70-4.30 (m, 4H), 4.35 (bs, 1H), 7.10 (d, 2H J=5 Hz), 8.55 (bs, 2H). Anal. calcd. for $C_7H_9NO_2$: C, 60.43 ; H, 6.48 ; N, 10.07. Found: C, 60.55; H, 6.69; N, 9.89.

Preparation of 4-(2-aminophenoxy)pyridine (4.22)

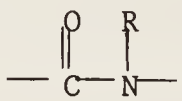
The same procedure as described above for compound (4.20) was used except phenol was replaced by 2-aminophenol, to give 2.85 g (76 %) of compound (4.22): m.p. 98°C; IR ($CHBr_3$) 3365, 3290 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.75 (b, 2H), 6.50-7.20 (m, 6H), 8.40 (d, 2H J=5 Hz). Anal. calcd. for $C_{11}H_{10}N_2O$: C, 70.97; H, 5.38; N, 15.05. Found: C, 70.65; H, 5.52; N, 14.95.

CHAPTER 5

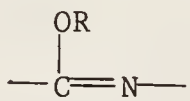
REARRANGEMENT IN AMIDES - OXYGEN TO NITROGEN MIGRATION OF ALKYL GROUPS

5.1. Introduction

An amide (5.1) is generally more stable than its isomeric imidate (5.2), as evidenced by chemical, physical and spectral investigations [63AHC311, 65OR1, 67HCA725, 65T1681, 64AHC36]. The greater stability of the amide has been rationalized on the basis of π-stabilization energy [65T2257, 67JAM4300, 66JOC3007] and σ-framework stabilization energy [63MI1]. However, for heterocyclic analogues of amides, such as pyridones, the difference in energy between the amide and the imidate form is smaller [68JAM1569]. The equilibrium between the amide and the imidate can be catalyzed thermally or by acids or alkyl halides.



(5.1)



(5.2)

The thermal rearrangement of 2-methoxypyridine to N-methyl-2-pyridone has been shown to be intermolecular [57JAM3160, 65JCS4911]. Although the earlier workers have

found the reaction to be catalyzed by benzoyl peroxide and that old samples of 2-methoxypyridine rearrange at a much faster rate than fresh samples (probably due to hydroperoxide formation) [57JAM3160], the later workers found very minor changes in the rate by adding benzoyl peroxide or benzoquinone to the reaction mixtures [65JCS4911]. For 4-methoxypyridine the oxygen to nitrogen methyl migration (Scheme 5.1) has been suggested to go through an intermolecular ion-pair type of intermediate [64MI1, 65JCS4911]. Acid and alkyl halides have been used as catalysts for oxygen to nitrogen migration [65JCS4911].

Scheme 5.1

Although oxygen to nitrogen migrations are generally thermodynamically favored, steric interactions can cause the O-substituted derivatives to predominate at equilibrium. For example, 4-methoxy-2,6-diphenylpyridine is more stable than 2,6-diphenyl-1-methyl-4-pyridone because of 1,2,6-steric interactions [68JAM1569]. Oxygen to nitrogen migrations have also been accomplished by heating with mercuric bromide and other Lewis acids [67CC122]. Oxygen to

nitrogen migration in 2-substituted pyridines with allyloxy-, methallyloxy- and crotyloxy- groups have been reported to go through a Claisen rearrangement to give N- and 3-substituted 2-pyridones [64JOC892]. An attempted rearrangement of 4-allyloxypyridine was unsuccessful [63JOC2885], however, in a benzfused system, 4-allyloxyquinoline, oxygen to nitrogen migration has been reported to go via a Claisen rearrangement [65JOC1986].

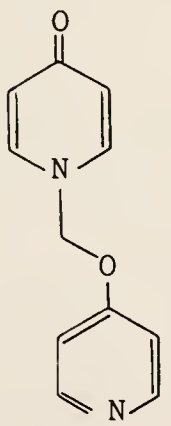
Although the thermal rearrangement of alkyl groups from oxygen to nitrogen in 4-alkoxypyridines has been proposed to be intermolecular [65JCS4911], there has been no conclusive experimental evidence.

5.2. Aim of the Work

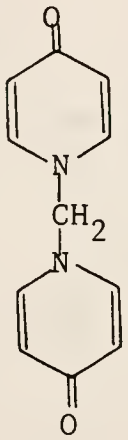
The alkyl group migrates from oxygen to nitrogen in 4-alkoxypyridines by heat and the migration has been found to be catalyzed by acids and alkyl halides [65JCS4911]. Although the mechanism in alkyl halide catalysis has been found to be intermolecular for the alkyl group migration from oxygen to nitrogen in 4-alkoxypyridines [68JAM1569] there has been no experimental evidence for the purely thermal uncatalyzed rearrangements. For simple acyclic

imidates, the thermal rearrangement of groups from oxygen to nitrogen known as Chapman rearrangement has been shown to be intramolecular for the aryl group migration and intermolecular for the alkyl group migration [70MI1, 61CR179, 72CC303].

As indicated earlier in Chapter 4, the thermal rearrangement of N-(4-pyridinoxymethyl)-4-pyridone (5.3) to bis N-(4-pyridonyl)methane (5.4) together with the availability of deuterium labelled compounds of (5.3) led to this work discussed in this chapter.



(5.3)



(5.4)

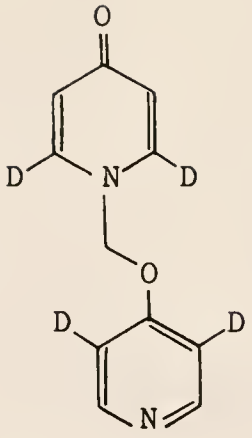
The aim of the present work was to study the nature of the thermal migration of the alkyl group in this selected 4-alkoxypyridine (5.3) and its suitably deuterated derivative, and use NMR and mass spectroscopic techniques to analyse the products, in particular to distinguish between inter- and intramolecular rearrangement.

5.3. Results and Discussion

The nature of migration, inter- or intramolecular, is generally elucidated by crossover experiments [85MI1]. The use of deuterated derivative in crossover experiments coupled with analysis of products by mass spectrometry makes it an elegant procedure to study the inter- or intramolecularity of the rearrangement [68JAM1569].

Choosing the compounds for crossover experiments requires (i) the two compounds must react at very similar rates, (ii) the migrating groups must have essentially equal reactivity towards either of the two reactants and (iii) quantitative estimation of any mixed products which are formed. The points (i) and (ii) were uniquely attained by labelling the starting compound both at the migrating as well as the non-migrating groups. Point (iii) was overcome by analysing the products by a mass spectrometer.

Here compounds chosen for the study were N-(4-pyridinoxymethyl)-4-pyridone (5.3) and its tetradeuterated derivative N-(3,5-dideutero-4-pyridinoxymethyl)-2,6-dideutero-4-pyridone (5.5).



(5.5)

Compound (5.3) and (5.5) were obtained as indicated in chapter 4. The exchange on compound (5.3) has to be carried out at 50°C to get compound (5.5), for if the exchange was carried out at room temperature it mainly gave N-(4-pyridinoxymethyl)-2,6-dideutero-4-pyridone (the mass spectrum (Figure 5.1) showed it to be 90% dideuterated). The mass spectrum of compound (5.5) showed it to be 30% tetradeuterated (Figure 5.1) (for further details about this exchange on compound (5.3) see chapter 4).

On heating at 200°C the alkyl group in compound (5.3) rearranges from oxygen to nitrogen forming bis N-(4-pyridonyl)methane (5.4) as the major product along with two

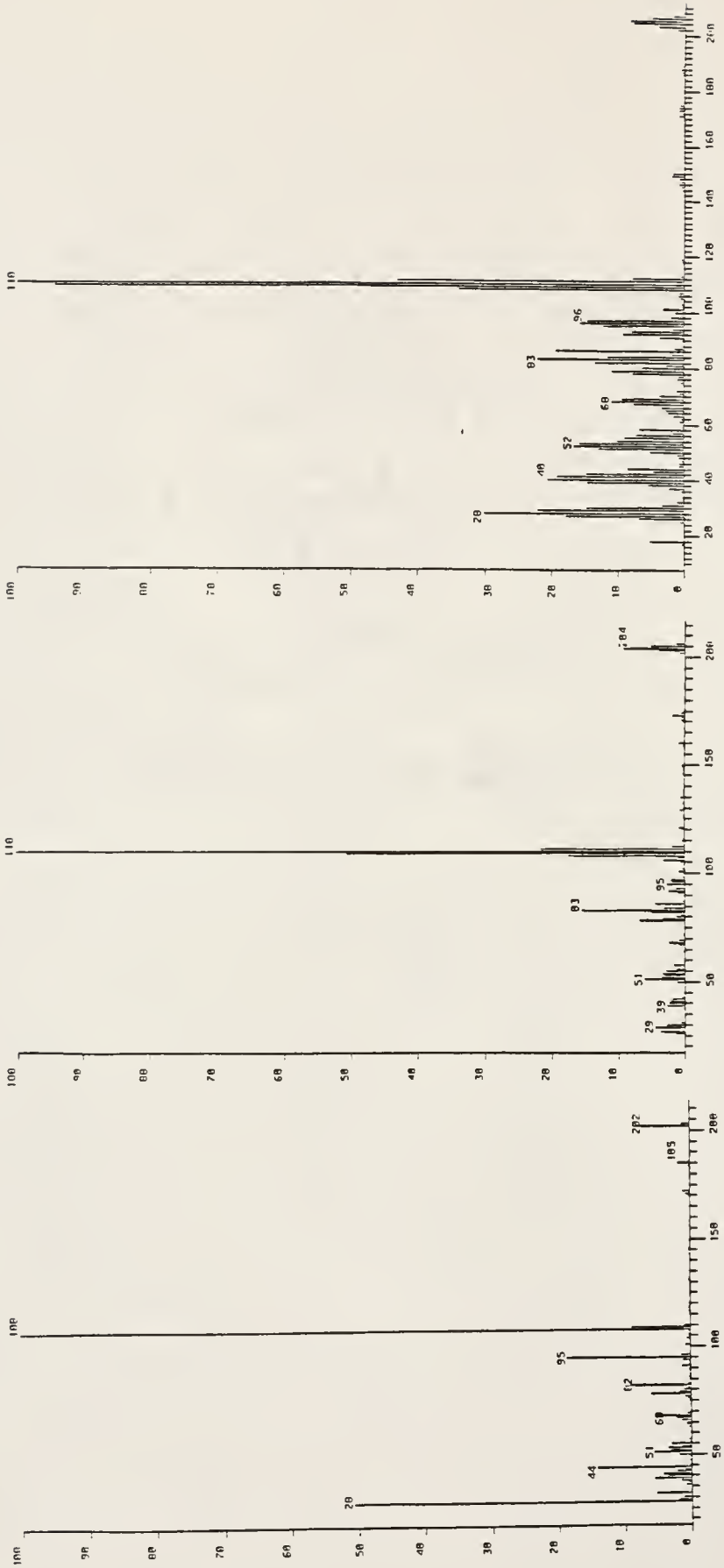
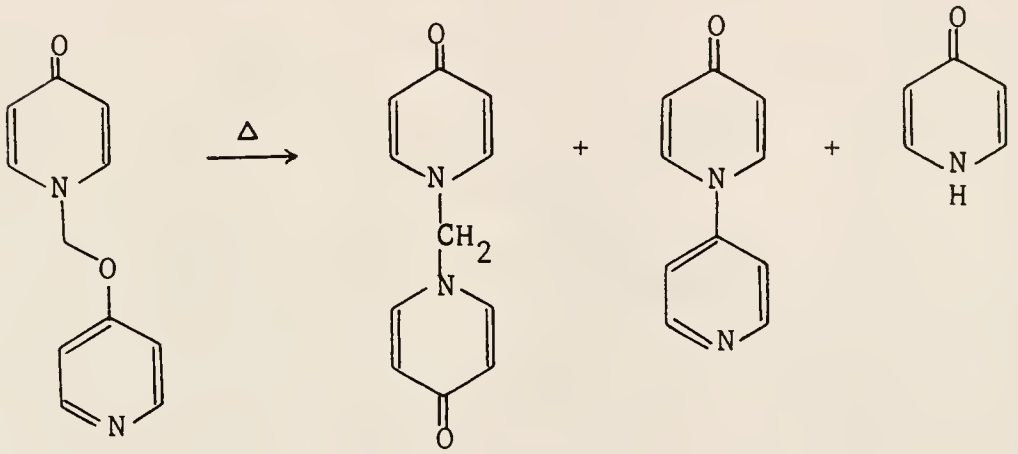


Fig. 5.1 Mass Spectrum of (a) N-(4-Pyridinoxymethyl)-4-pyridone (b) N-(4-Pyridinoxymethyl)-2,6-dideutero-4-pyridone and (c) N-(3,5-Dideutero-4-pyridinoxymethyl)-2,6-dideutero-4-pyridone.

minor products, N-(4-pyridyl)-4-pyridone (5.6) and 4-pyridone (scheme 5.2). The products were separated by column chromatography and identified by the usual analytical methods. For (5.6) the melting point and spectral data agreed with its literature values [76RC2167]. The ^{1}H NMR spectrum of the starting material (5.3) and the products (5.4) and (5.6) are given in Figures 5.2, 5.3 and 5.4 respectively.



(5.3) (5.4) (5.6)

Scheme 5.2

Since compound (5.3) has an N-substituted-4-pyridone ring it can, by resonance, act similar to an allyl group (5.7) and can undergo a cationic aza-Claisen rearrangement to (5.8), which are recently reported to be of great synthetic utility [83JAM6622, 83JAM6629], followed by another aza-Cope (Claisen) rearrangement to give bis N-(4-

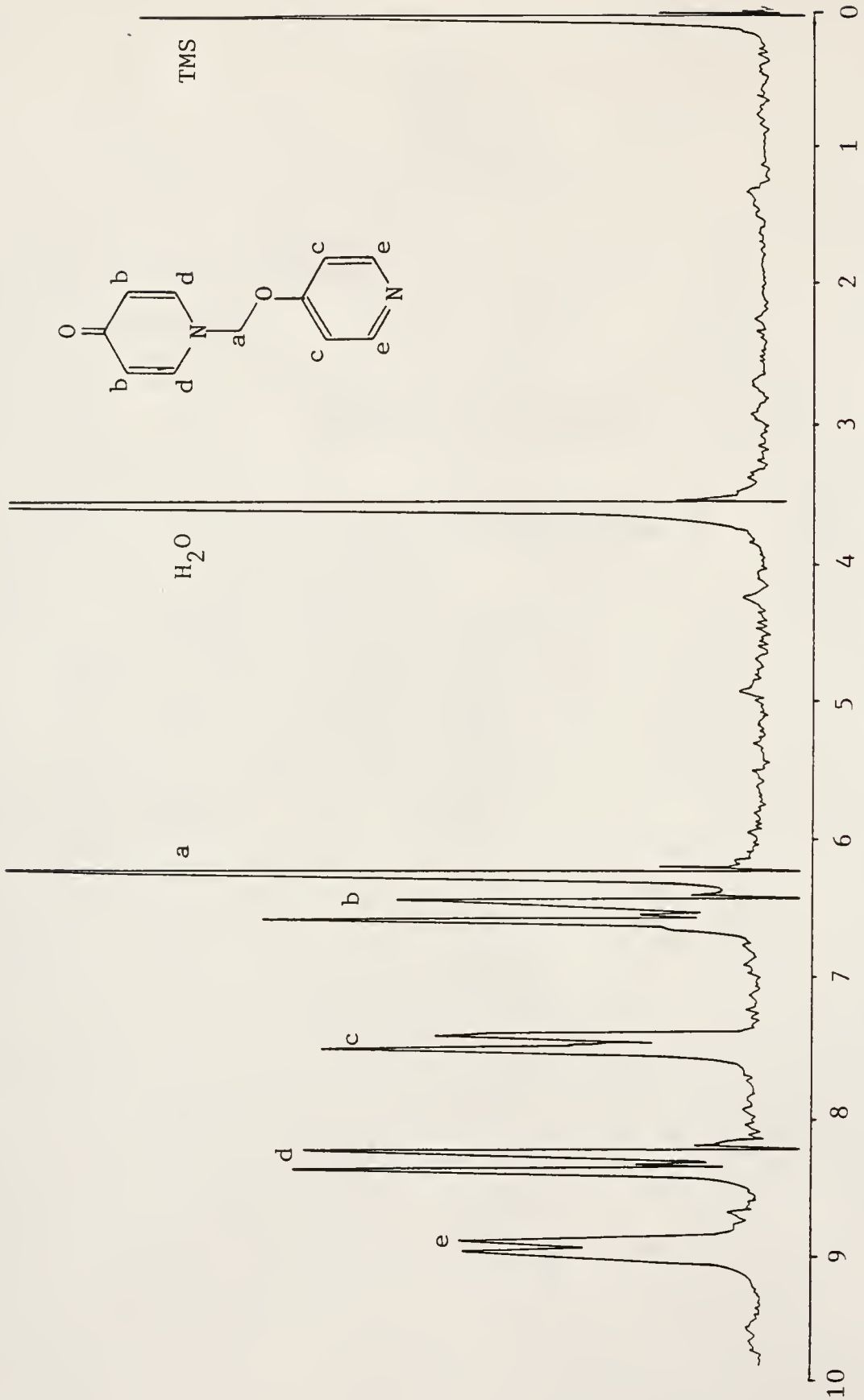


Fig. [illegible] 60 MHz ^1H NMR Spectrum of N-(4-Pyridinoxymethyl)-4-pyridone (in DMSO-d_6)

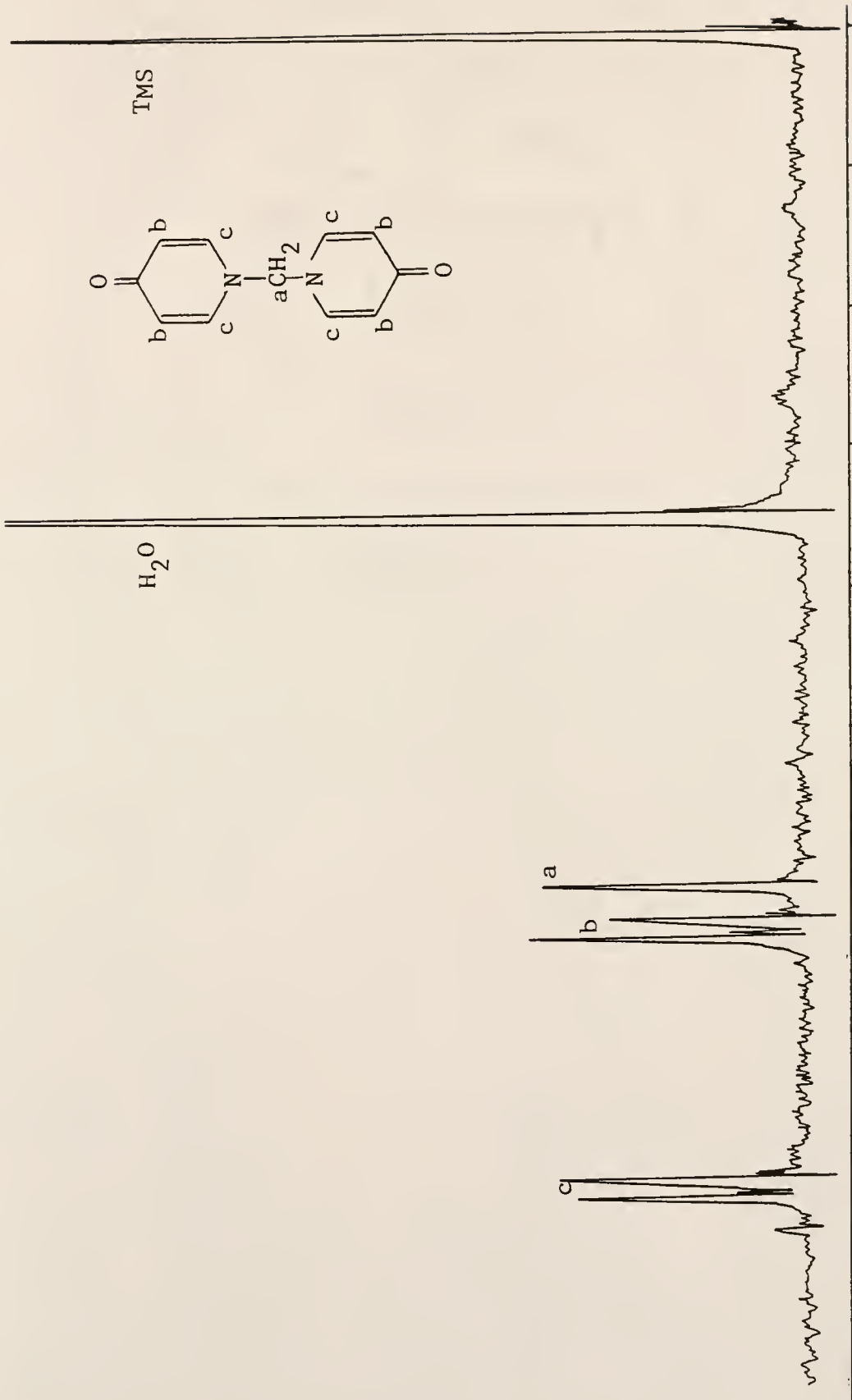


Fig. 3.3 60 MHz ^{1}H NMR Spectrum of the Major Product of Rearrangement - Bis(N-4-pyridonyl)methane (in DMSO-d_6).

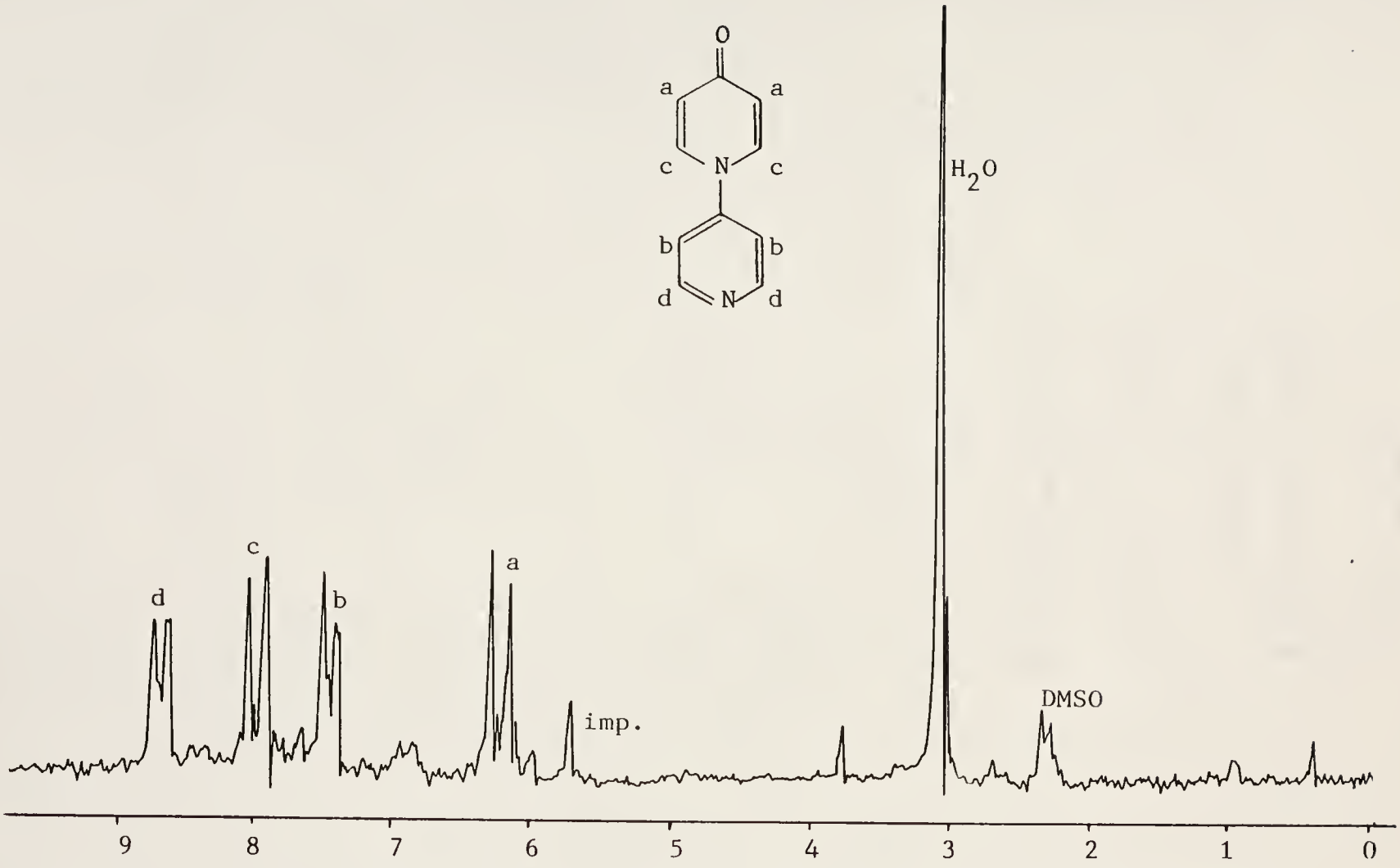
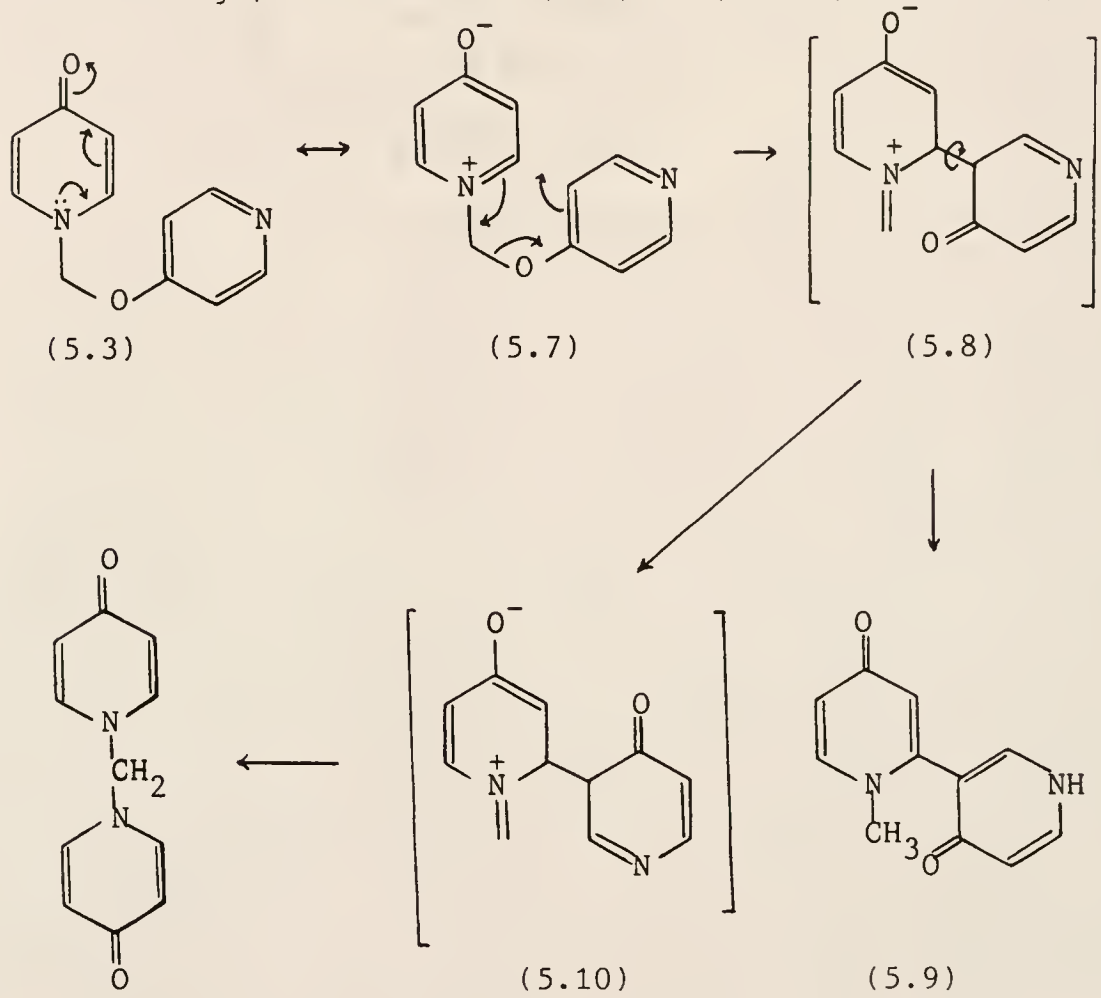


Fig. 4 60 MHz ^{1}H NMR Spectrum of the Minor Product Obtained - N-(4-Pyridyl)-4-pyridone (in DMSO-d_6).

pyridonyl)methane (5.4). The second rearrangement is possible only after a rotation around the bond connecting the two rings, that is from (5.8) to (5.10 (scheme 5.3).



(5.3) (5.7) (5.8)

(5.10) (5.9)

(5.4)

Scheme 5.3

From the thermolysis mixture of (5.3), no intermediate like (5.9) was isolated which should have been formed if it had gone through a Claisen rearrangement, unless the second Claisen rearrangement was much faster than the tautomeric equilibration process.

From examples reported in reviews on the Claisen rearrangement [77S589, 75OR1], of the two double bonds required for the rearrangement one was a non-aromatic double bond. Only two examples were reported in which the two double bonds were in the aromatic ring: benzyl phenyl ether and diphenylmethyl phenyl ether. On heating in suitable solvents such as quinoline these two compounds have been found to undergo homolysis rather than a Claisen rearrangement [60JCS1286].

5.3.1. Attempted Rearrangements by Chemical Methods

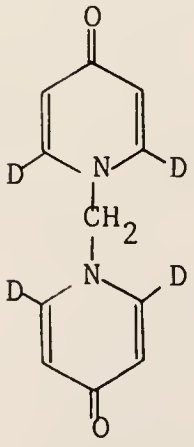
Zinc chloride (Lewis acid) and 4-toluenesulfonic acid (acid) were found to catalyze the oxygen to nitrogen migration in compound (5.3). Zinc chloride catalyzed the rearrangement and reduced the rearrangement temperature by 40°C whereas 4-toluenesulfonic acid catalyzed the rearrangement even in refluxing benzene. Acids and Lewis acids catalysis is common for Claisen rearrangements [83JAM6622, 77S589, 75OR1] as well as oxygen to nitrogen migration of alkyl groups in pyridones [65JCS4911, 67CC122].

An attempt was made to test the possiblity of Claisen rearrangement by introducing a phenyl ring in place of the pyridine ring. Such a compound N-(phenoxymethyl)-4-pyridone

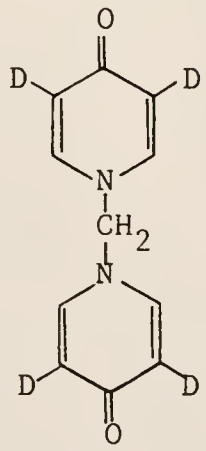
(5.11) was prepared as indicated earlier in chapter 4, however (5.11) on thermolysis gave either the starting material back or uncharacterizable tarry products.

5.3.2. Elucidation of Mechanism of Rearrangement by Physical Methods

In either compound (5.3) or (5.5) only if the cleavage was between $-O-CH_2-$ it can lead to the rearranged product unless it was a radical reaction, which was found not to be the case since the reaction was catalyzed by Lewis acids. That was why with compound (5.5) products of the type (5.12) and (5.13) were not formed, as seen from the 200 MHz ^1H NMR spectrum.



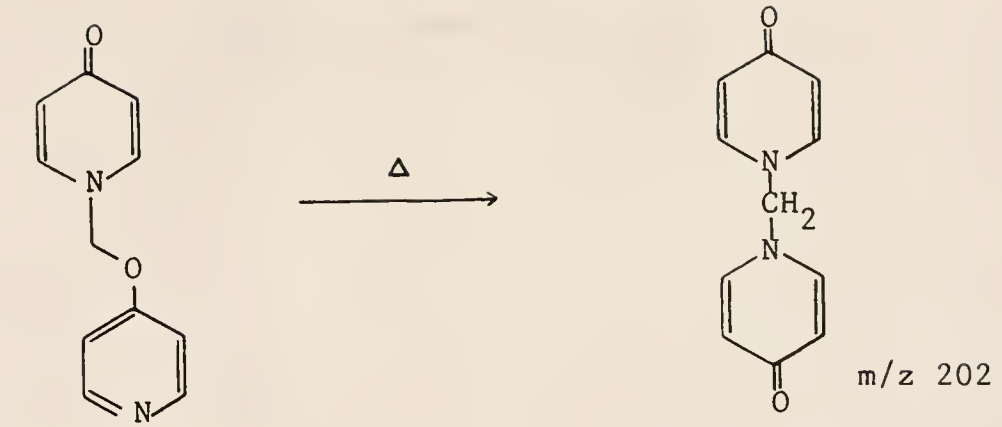
(5.12)



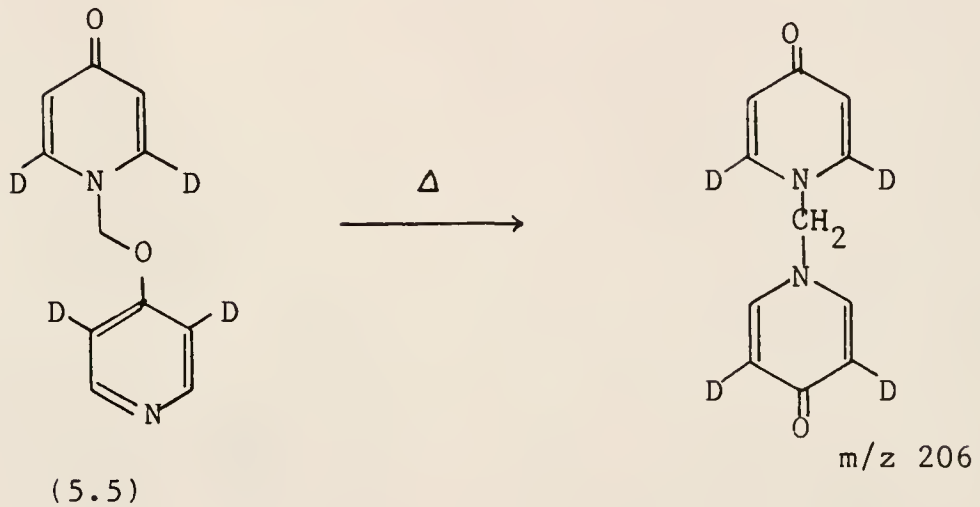
(5.13)

A detailed analysis of the 200 MHz ^{1}H NMR spectra of the products obtained from the thermolysis of (i) compound (5.3), (ii) compound (5.5) and (iii) an equimolar mixture of compounds (5.3) and (5.5) did not reveal any clue to the inter- or intramolecular nature of the migration.

Hence, in order to distinguish the inter- or intramolecularity of the reaction, the products were analyzed by mass spectrometry. From the molecular ion peak intensities, it should be possible to say if the migration was inter- or intramolecular. For example, if for compound (5.3) the molecular ion of the rearranged product is M, then for compound (5.5) it would be M+4. Now if the migration was just intramolecular then molecular ion peaks of M and M+4 would be seen. On the other hand if it was intermolecular then molecular ion peaks at M, M+2 and M+4 would be observed. An exact picture would be also to consider the isotope peak intensities of the molecular ions. So an analysis of peak intensities in the region of 202 to 208 in the mass spectra of products obtained on heating at 200°C from (i) compound (5.3) alone (Scheme 5.4), (ii) compound (5.5) alone (Scheme 5.4) and (iii) compounds (5.3) and (5.5) together (Scheme 5.5), would reveal the inter- or intramolecularity of the reaction.

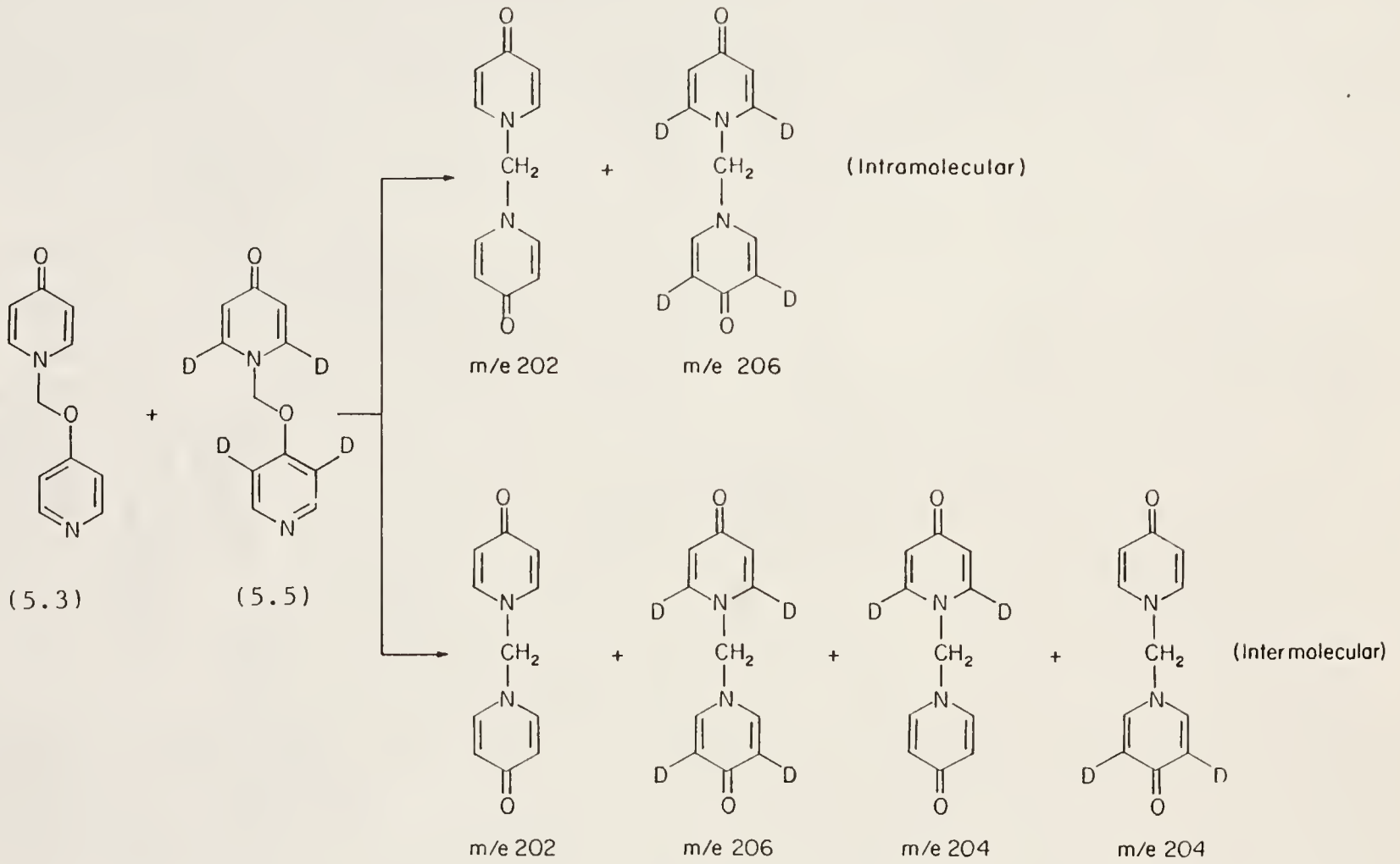


(5.3) Scheme 5.4 (5.4)



(5.5)

The mass spectral data for the molecular ion of the products of the three reactions are given in Table 5.1. From entries (i) and (ii) of Table 5.1 it is seen that only entry (ii) has peaks from m/z 205 - 208. So if the rearrangement was occurring intramolecularly then the peaks from m/z 205 - 208 would also have the same ratio of peak intensities. From Table 5.1 the peak intensities were calculated for an intramolecular migration in (iii) for


(5.3)
(5.5)
m/e 202
m/e 206
(Intramolecular)
m/e 202
m/e 206
m/e 204
m/e 204
(Intermolecular)

Scheme 5.5

compound (5.5) with reference to (ii) and keeping the peak intensity of m/z 205 as the standard. The values are given in entry (i) of Table 5.2. Subtracting entry (i) of Table 5.2 from entry (iii) of Table 5.1 gave the values given in entry (ii) of Table 5.2. From Table 5.1 the peak intensities were calculated for an intramolecular migration in (iii) for compound (5.3) with reference to (i) and keeping the peak intensity of m/z 402 in entry (ii) of Table 5.2 as the standard. The values are given in entry (iii) of Table 5.2. Subtracting entry (iii) from (ii) in Table 5.2 gave the difference between the calculated, based on an intramolecular migration, and the experimentally observed peak intensities. The magnitude of the difference in intensities reveal that there was an appreciable increase in intensity for the M+2 peak clearly indicating that the rearrangement was intermolecular.

The magnitude of difference (2.6) for the peak at m/z 204 was found to be 23% of the intensity calculated for an intramolecular rearrangement for the same peak at m/z 204.

The same results were also obtained by considering a complete intermolecular rearrangement and calculating the intensities. If the rearrangement was completely (100%) intermolecular then the products formed for entry (iii) of Table 5.1 would be as indicated below:

(5.3) + monodeuterated compound --> monodeuterated product
+ (5.4)

(5.3) + dideuterated compound --> monodeuterated product
+ dideuterated prodct

(5.3) + trideuterated compound --> monodeuterated prodcut
+ dideuterated prodcut

(5.3) + (5.5) --> dideuterated product

The mono-, di- and trideuterated compounds mentioned above are the partially deuterated compounds present along with compound (5.5). From the products formed as shown above it is clear that no tri- or tetradeuterated compounds are formed. So peaks at m/z 205 and 206 should have intensity only as that for the M+1 and M+2 peaks of the molecular ion peak at m/z 204 which was calculated to be 12.8% and 1.1%, respectively of the intensity of molecular ion peak at m/z 204.

Considering the peak intensity (13.7) for m/z 204 in entry (iii) of Table 5.1 as 100, the equivalent of 12.8% was calculated to be 1.7. Now subtracting this value of 1.7 for m/z 205 from the corresponding peak intensity in entry (iii) of Table 5.1 the value 9.1 was obtained.

From the calculated value for 100% intermolecular migration (1.7) and the excess intensity observed (9.1 - obtained by subtracting the calculated value (1.7) from the experimentally observed value (10.8) given in entry (iii) of Table 5.1 for the peak at m/z 205) it was found that the excess in intensity was 81% of the calculated value.

Compounds (5.3) and (5.5) are solids and the rearrangement occurred at 200°C when the solids began to melt. At this stage there exists a possiblity of inhomogenity in the mixtrue. Since intermolecular migrations are very much dependent on the environment around a molecule the inhomogeneity in the melt of the mixture might explain the formation of intermolecularly rearranged product only to a lesser extent as seen above from the calculations done.

Another strong evidence against an intramoleuclar rearrangement was that the product (5.9) was not detected in the mass spectrometer. If this product was formed then there would have been peaks observed at m/z 201 (with loss of hydrogen atom) and at m/z 187 (with loss of methyl group), which was not observed in the mass spectrum of the product (Figrue 5.5).

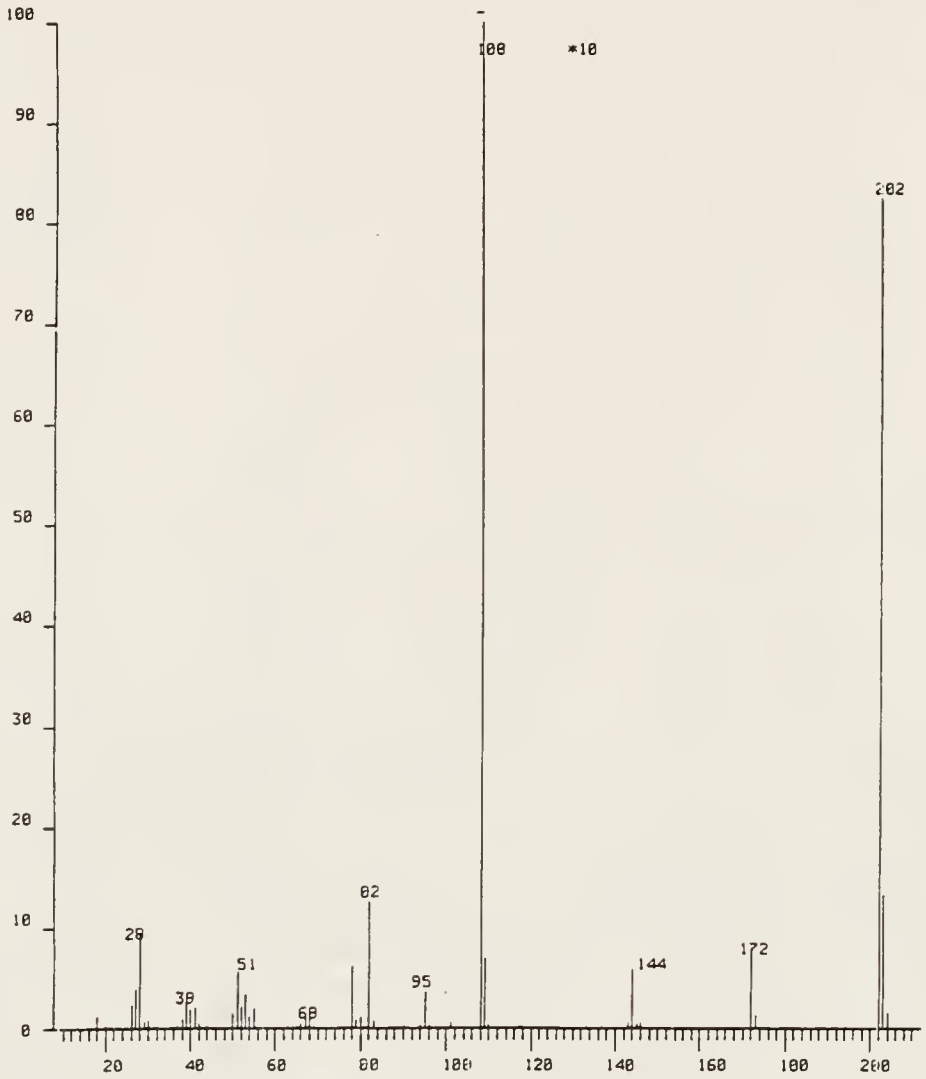


Fig. 5.5 Mass Spectrum of the Rearranged Product Obtained from N-(4-Pyridinoxymethyl)-4-pyridone.

Fig. 5.6 Mass Spectrum of the Rearranged Product Obtained from N-(3,5-Dideutero-4-pyridinoxymethyl)-2,6-dideutero-4-pyridone.

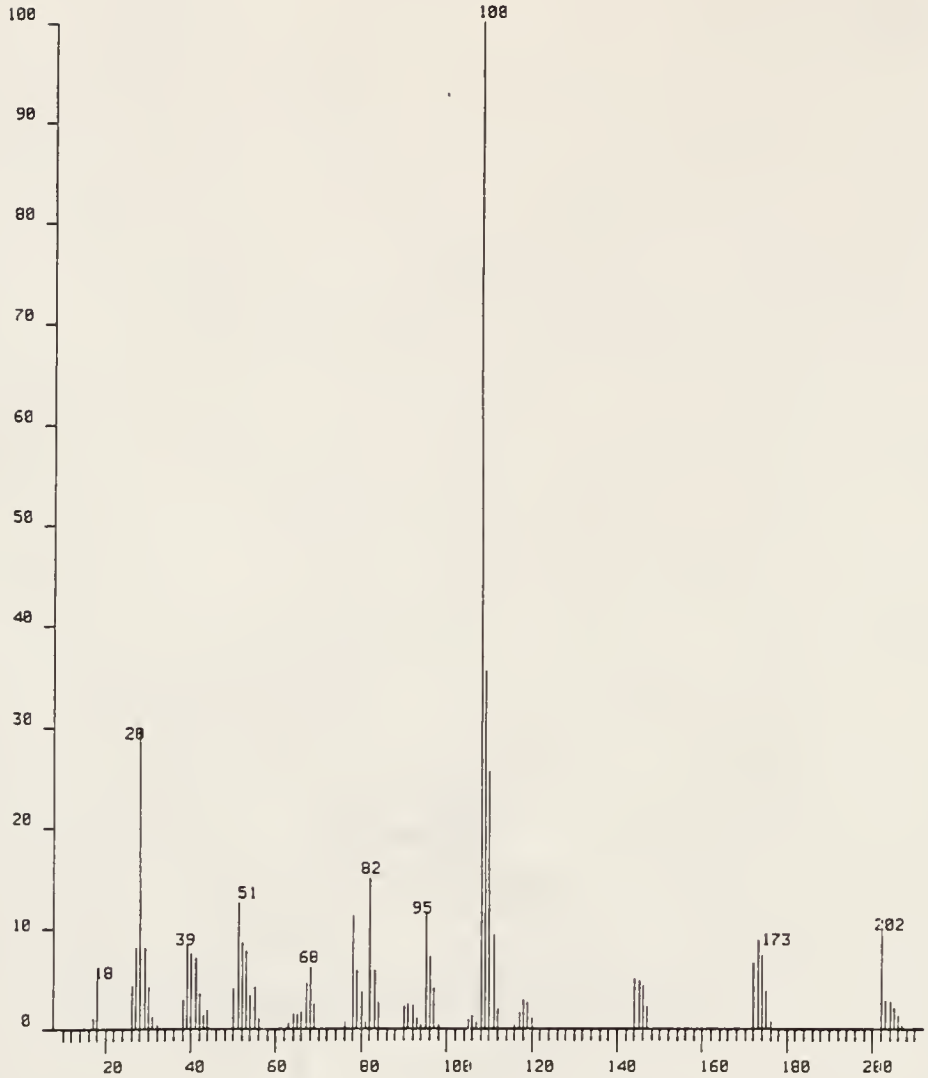


Fig. 5.7 Mass Spectrum of the Rearranged Product Obtained from a Mixture of N-(4-Pyridinoxymethyl)-4-pyridone and N-(3,5-dideutero-4-pyridinoxymethyl)-2,6-dideutero-4-pyridone.

Table 5.1 Mass Spectral Peak Intensities of the Molecular Ions[a] for the Rearranged Products from (5.3), (5.5) and a Mixture of (5.3) and (5.5).

m/z	202	203	204	205	206	207	208
(i)[b]	85.3	13.7	1.5	-	-	-	-
(ii)[c]	2.9	14.6	27.5	30.1	17.4	6.1	1.5
(iii)[d]	52.4	14.3	13.7	10.8	6.9	1.9	-

[a] The peak intensities are given in percentage to the total intensity of all the peaks between m/z 202 - 208 found in a thermolysis product.

[b] Thermolysis product of compound (5.3) alone.

[c] Thermolysis product of compound (5.5) alone.

[d] Thermolysis product of a mixture of compounds (5.3) and (5.5) together.

5.4. Conclusions

The thermal rearrangement of alkyl group, for an alkoxypyridine, from oxygen to nitrogen had been experimentally established to be intermolecular which was similar to the acid as well as the alkyl halide catalyzed alkyl migrations [65JCS4911].

This work also indicates how powerful a tool a labelled compound could be in decifering the mechanism of a reaction.

Table 5.2 Calculated Mass Spectral Peak Intensities[a] and the Difference Between the Calculated and Experimental Mass Spectral Peak Intensities.

m/z	202	203	204	205	206	207	208
(i)[b]	1.6	5.5	10.3	10.8	6.5	2.7	0.7
(ii)[c]	50.8	8.8	3.4	-	0.4	-0.8	-0.7
(iii)[d]	50.8	7.9	0.8	-	-	-	-
Difference	-	0.9	2.6	-	0.4	-0.8	-0.7

[a] See foot note 'a' for Table 5.1.

[b] Calculated for an intramolecular migration from (ii) of Table 5.1 and m/z 205 peak in (iii) of Table 5.1 as reference.

[c] Obtained by subtracting entry (i) of this table from entry (iii) of Table 5.1.

[d] Calculated for an intramolecular migration from entry (i) of Table 5.1 and m/z 202 peak in (ii) of this Table as reference.

5.5. Experimental

Melting points were recorded on a Bristoline hot-stage microscope and are uncorrected. The ^{1}H NMR spectra were recorded on a Varian 360L spectrometer using TMS as the

internal reference and ^{13}C NMR spectra were recorded on a JEOL FX 100 spectrometer and Varian XL 200 spectrometer using the solvent (DMSO-d_6) peak as the reference. The IR spectra were obtained on a Perkin-Elmer 283 B spectrophotometer.

5.5.1. Rearrangement of Alkyl Group from Oxygen to Nitrogen in 4-Pyridones - General Procedure

The pyridone (5.3) or (5.5) or a mixture of (5.3) and (5.5) (200 mg) was heated at 200°C for 25 minutes after which the dark mass was stirred with chloroform and filtered, gave 160 mg (80%) of the corresponding bis N-(4-pyridonyl)methane: m.p. >350°C and used directly for mass spectral analysis (Figures 5.5, 5.6 and 5.7).

5.5.2. Preparation of N-(3,5-Dideutero-4-pyridinoxymethyl)-2,6-dideutero-4-pyridone (5.5)

The pyridone (5.3) (100 mg) was dissolved in DMSO-d_6 (0.5 mL) and sodium deuteroxide (1M 1mL) was added to this solution. The mixture was kept overnight at 50°C, cooled and then poured into ice cold deuterium oxide (2 mL). The solid formed was filtered and dried, giving 92 mg (90%) of pyridone (5.5). This was directly used for the rearrangement and the mass spectrum (Figure 5.4) showed the product to be 30% tetradeuterated.

CHAPTER 6

SUMMARY

A general introduction about the structure and properties of amides pertaining to this work was given in chapter 1. Preparation of acyclic, cyclic and vinylogous amides was discussed. The scope of this work was also mentioned.

The synergistic effect of amide groups for α-metallation was discussed in chapter 2. 1,3-Diacylimidazolidines, 1,3-diacylhexahydropyrimidines and 1,3,5-triacylhexahydro-sym-triazines were reacted with lithiating reagents and this was followed by treatment with electrophiles. However, they did not show any additional increase in carbanion stability compared with those reported for N-acylpyrrolidines and N-acylpiperidines, respectively. The fact that the second amide group did not bring about any substantial additional stabilization of the carbanion might have been either due to (i) the most favored conformation of the diacyl amines had the R group of one of the acyl unit sterically hindering the attack at the methylene of the N-CH_2-N unit or (ii) the conformer favoring the double

stabilization was not the predominant conformer. 1,3-Dipivaloylimidazolidine did not react under lithiating conditions. However, 1,3-dibenzoylimidazolidine, 1,3-dibenzoyl- and 1,3-dipivaloylhexahydropyrimidine, 1,3,5-Tribenzoylhexahydro-sym-triazine and 1,3,5-tripivaloylhexahydro-sym-triazine showed reaction under lithiating conditions.

In chapter 3 the NMR study (equilibria and kinetics) of bis- and tris-amides was discussed. 1,3-Dibenzoylimidazolidine, 1,3-dipivaloylimidazolidine and 1,3-dibenzoylhexahydropyrimidine showed signals in their low temperature ^{1}H NMR spectra for all of the three conformers. However, even at very low temperatures, 1,3-dipivaloylhexahydropyrimidine showed signals for only two conformers. The signal for the conformer with two pivaloyl groups on the same side was not observed.

In 1,3,5-tribenzoylhexahydro-sym-triazine the two conformers were observed in the low temperature ^{1}H NMR spectrum. However, even at very low temperatures for 1,3,5-tripivaloylhexahydro-sym-triazine only one conformer was observed (in agreement with that observed for 1,3-dipivaloylhexahydropyrimidine).

In conformer population the ^{13}C NMR spectra of all amides agreed with their corresponding ^{1}H NMR spectral data

except that the signals for the least populated conformers were not observed.

The relative energy difference between the different conformers was calculated from the population ratios obtained. All amides except 1,3,5-tripivaloylhexahydro-sym-triazine showed only one coalescence temperature. The energy of activation for the barrier to rotation around amide C(O)-N bonds was calculated from the coalescence temperature. The energy, in general, for benzamides, was around 15 kcal $mole^{-1}$ and for pivalamides, around 10 kcal $mole^{-1}$.

The mechanism of rotation of the amide groups from their spectral behavior was discussed. The rotations will be either individual or concerted (same or different direction). For 1,3,5-tripivaloylhexahydro-sym-triazine, only one conformational isomer (the symmetrical) was observed indicating that in that molecule the rotation around the amide C(O)-N bonds may be concerted (or correlated) or the rotations may be sequential with the unsymmetrical conformational isomer as a short lived intermediate in the transition state of the topomerization process of the symmetrical conformational isomer. Furthermore, it was speculated for 1,3,5-tripivaloylhexahydro-sym-triazine, the least energetic process for topomerization of the symmetrical conformational

isomer would be that in which two amide bonds rotate in one direction while the third one rotates in the opposite direction.

The hydrogen-deuterium (H/D) exchange behavior of different N- and O- substituted vinylogous amides, such as the 4-pyridones, was discussed in chapter 4. The main aim was to explain the ambient temperature hydrogen deuterium exchange at the 3,5-positions of the pyridine ring in N-(4-pyridinoxymethyl)-4-pyridone. A number of N-substituted 4-pyridones and O-substituted 4-oxypyridines were investigated.

It was found that a heteroatom (O, S) at the β-position of the N-alkyl side chain increased the H/D exchange rate of the 2,6-protons five fold compared to N-methyl-4-pyridone. And also a heteroatom with an exchangeable hydrogen or an acidic C-H at the γ-position of the O-alkyl side chain increased the H/D exchange rate of the 3,5-protons compared to 4-methoxypyridine.

The mechanistic study of alkyl group migration from oxygen to nitrogen in vinylogous amides, such as the 4-pyridones, was discussed in chapter 5. The rearrangement of N-(4-pyridinoxymethyl)-4-pyridone at 200^{o}C gave bis(N-4-pyridonyl)methane. The rearrangement products from (i) N-(4-pyridinoxymethyl)-4-pyridone, (ii) N-(3,5-dideutero-4-

pyridinoxymethyl)-2,6-dideutero-4-pyridone and (iii) a mixture of N-(4-pyridinoxymethyl)-4-pyridone and N-(3,5-didetuero-4-pyridinoxymethyl)-2,6-didetuero-4-pyridone, were analysed by mass spectrometry. The molecular ion peaks (from m/z 202 to 208) of (i) and (ii) were used to calculate the intensities of the molecular ion peaks for (iii) and compared with the experimentally observed values. The comparison showed a large increase at m/z 204, indicating that the thermal rearrangement of alkyl groups from oxygen to nitrogen in 4-alkoxypyridines was intermolecular.

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Letter Codes for Journal Titles

Code	Full Title
A	Ann. Chim.
ACR	Acc. Chem. Res.
AG(E)	Angew. Chem. Int. Ed. Engl.
AHC	Adv. Heterocycl. Chem.
AJC	Aust. J. Chem.
BCSJ	Bull. Chem. Soc. Japan
BP	Biopolymers

CB	Chem. Ber.
CC	J. Chem. Soc. Chem. Commun.
CI	Chem. Ind.
CJC	Can. J. Chem.
CR	Chem. Rev.
GCI	Gazz. Chim. Ital.
HCA	Helv. Chim. Acta.
JAM	J. Am. Chem. Soc.
JCP	J. Chem. Phys.
JCS	J. Chem. Soc.
JCS(B)	J. Chem. Soc. (B)
JCS(P1)	J. Chem. Soc. Perkin Trans. 1
JCS(P2)	J. Chem. Soc. Perkin Trans. 2
JHC	J. Heterocycl. Chem.
JMR	J. Mag. Reson.
JOC	J. Org. chem.
JOM	J. Organomet. Chem.
JPC	J. Phys. Chem.
M	Monatsh. Chem.
MI	Miscellaneous [book/journal]
MM	Macromoleucles
OMR	Org. Mag. Reson.
OR	Org. React.
RC	Rocz. Chim.
S	Synthesis
T	Tetrahedron
TL	Tetrahedron Lett.

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BIOGRAPHICAL SKETCH

Ramiah Murugan was born on July 30, 1956 at Madurai, a city in Tamil Nadu state in India. He received his Bachelor of Science (special) degree in chemistry from American College (affiliated to Madurai University) in April 1975. Then he received his Master of Science degree in chemistry (with specialization in organic chemistry) from the School of Chemistry of Madurai University in April 1977. He was awarded a gold medal for securing the first rank in the University. From November 1977 to May 1978 he received a CSIR Junior Research Fellowship from the Government of India. From June 1978 to December 1981 he served as Junior Scientist at University Service and Instrumentation Centre of Madurai University, during which time he was in charge of the Analytical Division and was also teaching organic spectroscopy to Master of Science students. He entered the graduate programme in chemistry at the University of Florida in January 1982 to work towards his Ph. D.

He has an elder sister, two younger sisters and four younger brothers. He is married to Sutharchana Devi and has one daughter Meenasarani Linde.

I certify that I have read this study and that in my opinion it confirms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Alan R. Katritzky, Chairman
Professor of Chemistry

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William R. Dolbier, Jr.
Professor of Chemistry

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William M. Jones
Professor of Chemistry

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Professor of Chemistry

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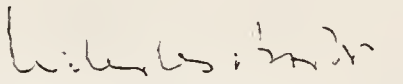

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This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

May, 1987

Dean, Graduate School

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